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# Efficacy and Safety of Combination Pharmacotherapy for Patients with Overactive Bladder: A Rapid Evidence Assessment

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## Abstract

***Context:*** Oral pharmacotherapy consisting of antimuscarinics, β3-adrenoreceptor agonists, or combinations of these agents forms the mainstay of overactive bladder (OAB) management.
***Objective:*** To evaluate the efficacy and safety of combination therapy in patients with OAB.
***Evidence acquisition:*** A literature search was conducted in June 2018 using Embase, MEDLINE, and Cochrane databases via Ovid and relevant congress abstracts. Studies reporting the efficacy/safety of two antimuscarinics or a β3-adrenoreceptor agonist plus an antimuscarinic were included.
***Evidence synthesis:*** Publications reported on clinical efficacy, safety, and health-related quality of life (HRQoL) for mirabegron (M) plus solifenacin (S) from three 12-wk randomised controlled trials (RCTs)—SYMPHONY, SYNERGY, and BESIDE—and a 12-mo RCT, SYNERGY II. SYMPHONY reported statistically significant improvements in clinical symptoms and HRQoL with combination therapy versus solifenacin 5 mg (S5) and placebo. In SYNERGY, there were consistent improvements in urinary incontinence (UI) episodes/24 h and micturitions/24 h (coprimary endpoints), and in secondary efficacy parameters with mirabegron 25 mg (M25) + S5 and mirabegron 50 mg (M50) + S5 versus respective monotherapies. In patients with an inadequate response to S5 monotherapy (BESIDE), greater improvements in UI (primary endpoint) were noted for M50 + S5 versus S5 ($p = 0.001$). Combination therapy was noninferior to solifenacin 10 mg (S10) for reduction in UI and superior to S10 for improvement in micturition frequency ($p < 0.001$), and resulted in greater improvements from baseline in OAB-5 Dimension scores versus S5 and S10 ($p < 0.01$). In SYNERGY II, clinically meaningful and sustained improvements in clinical outcomes were observed for M50 + S5 versus M50 or S5. Combination therapy was well tolerated in all four trials. The incidence of adverse events (AEs) was similar across groups, and there were no notable differences in the incidence of specific AEs. Positive efficacy outcomes were observed in five studies of dual antimuscarinic therapy (trospium + solifenacin).

† Address at the time the rapid evidence assessment was undertaken.
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***Conclusions:*** Mirabegron plus solifenacin provides effective, well-tolerated treatment for patients with OAB. Limited data for dual antimuscarinic therapy suggest a benefit in patients with moderate-to-severe symptoms.
***Patient summary:*** Overactive bladder (OAB) is treated with medicines called antimuscarinics, such as solifenacin, propiverine, or trospium, or another β-adrenoreceptor agonist medicine called mirabegron, which works in a different way. We looked at published scientific studies of patients with OAB treated with mirabegron plus solifenacin together, or with two antimuscarinics. We found that mirabegron plus solifenacin can help reduce symptoms and improve quality of life. Patients tolerate this treatment well, with few patients experiencing side effects.


## 1. Introduction

Overactive bladder (OAB) is characterised by urinary urgency, generally accompanied by increased voiding frequency and nocturia, with or without incontinence, in the absence of urinary tract infection (UTI) or other obvious pathology [1,2]. Reports of OAB prevalence range from 11.8% to 35.6% in the USA and Europe, based on four large population-based surveys [3], with more women than men being affected [4]. OAB symptoms are generally persistent and can have an adverse effect on health-related quality of life (HRQoL).

Oral pharmacotherapies for OAB/urinary incontinence (UI) consist of antimuscarinics (eg, solifenacin, propiverine, and trospium) and a β3-adrenoreceptor agonist (mirabegron) [5]. Mirabegron and antimuscarinic agents have similar efficacy, but mirabegron has a more favourable tolerability profile, particularly relating to anticholinergic effects such as dry mouth, constipation, and blurred vision [6]. Some patients do not achieve sufficient improvement in symptoms with antimuscarinic agents, but increasing the dose may lead to increased adverse events (AEs). Furthermore, particularly in elderly patients who may already be receiving other anticholinergic medications, antimuscarinic therapy may increase the anticholinergic burden [7]. Combination therapy involving mirabegron and an antimuscarinic is therefore an attractive option.

Recent guidelines from the European Association of Urology (EAU) [5], the American Urological Association (AUA) [8], and the Canadian Urological Association [9] recommend antimuscarinic or mirabegron monotherapy as a first- or second-line option for the management of OAB/UI, and combination therapy with mirabegron plus antimuscarinics in patients whose symptoms are refractory to monotherapy. As the efficacy and safety of dual antimuscarinic therapy have also been reported [10–12], this literature review aimed to identify the evidence for the efficacy and safety of combination therapy with either mirabegron and an antimuscarinic agent or two antimuscarinics.

## 2. Evidence acquisition

This rapid evidence assessment [13] consisted of a systematic literature search, conducted on June 7, 2018 in Embase, MEDLINE, and Cochrane via Ovid, as well as the Cochrane Central Trials Register and Database of Systematic Reviews and other Cochrane Library assets, using terms related to the disease, treatments of interest, and relevant treatment outcomes including efficacy, safety, and patient-reported outcomes (PROs) including HRQoL. There was no date restriction, and studies not published in English were excluded. Abstracts published from June 2016 to June 2018 for four international meetings were also searched: EAU, AUA, International Continence Society, and International Urogynecological Association. In addition, bibliographies of the included studies were manually searched to identify any further publications. Searches were performed by one researcher and reviewed by a second researcher. All publications reporting clinical outcomes (efficacy/effectiveness and safety) for clinical trials beyond and including phase II or observational studies of combination treatment involving mirabegron and an antimuscarinic agent or two antimuscarinic agents in patients with OAB were included. The search was performed according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Fig. 1). Data from all the selected references were extracted into an agreed extraction grid by one researcher and reviewed by a second researcher. The quality assessment of included publications was performed using a simplified version of the GRADE scoring system [14]. See Supplementary Table S1 for further details on methodology.

## 3. Evidence synthesis

### 3.1. Study selection

Electronic searches from databases provided 3090 hits, and seven articles were identified through manual searches. Twenty-one publications (20 full publications [10–12,15–31] and one conference abstract [32]) met the inclusion criteria and are included in this review (Fig. 1). The GRADE quality assessment indicated that one study was of high quality [20], 14 were of moderate quality [12,15–19,21–25,28,29,31], and six were of low quality [10,11,26,27,30,32] (Supplementary Table S2). Of 16 publications reporting the results of mirabegron and solifenacin combination/add-on therapy, 14 were from five sponsored trials [15–22,26,28–32] and two [24,25] were from independent studies; primary data are summarised in Tables 1 and 2. A further five publications reported the efficacy and safety of dual antimuscarinic therapy, trospium plus solifenacin, in patients with moderate versus severe symptoms [10–12,23,25]. See

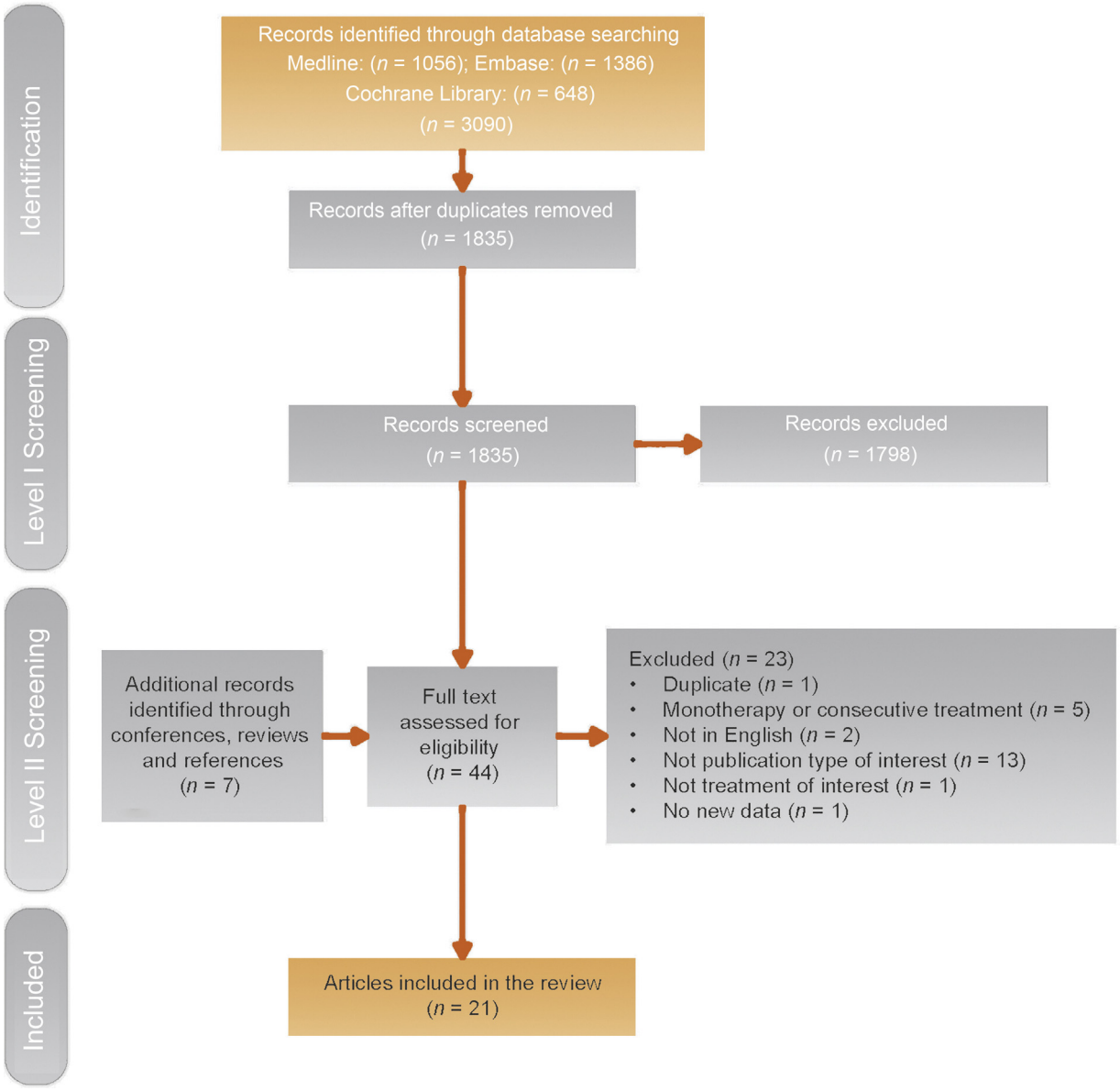


**Fig. 1 – Flow diagram for identification and selection of literature related to the combination therapy for treatment of patients with overactive bladder (OAB) using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).**

the extraction in Supplementary Table S3 for further details of these studies.

### 3.2. *Phase II trial of mirabegron plus solifenacin*

SYMPHONY [16] was a 12-wk, phase II, randomised, double-blind, placebo- and monotherapy-controlled, dose-ranging trial that explored the efficacy, dose-response relationship, and safety/tolerability of solifenacin plus mirabegron (S + M) combinations versus solifenacin monotherapy in adults ($N = 1307$) with OAB symptoms. The study involved 12 treatment groups: six combination groups (solifenacin 2.5, 5, or 10 mg [S2.5/5/10] + mirabegron 25 or 50 mg [M25/50]), five monotherapies (S2.5/5/10 or M25/50), and placebo.

Compared with S5 monotherapy, all combinations with S5 or S10 significantly ($p < 0.05$) improved mean volume voided (MVV) per micturition (primary endpoint), and three combinations (S10 + M25, S5 + M50, and S10 + M50) reduced micturition frequency from baseline to the end of treatment (EoT). All combination regimens except for S2.5 + M25 reduced urgency episodes significantly versus S5. No dose-related trends in treatment-emergent adverse event (TEAEs), blood pressure (BP), pulse rate, postvoid residual (PVR) volume, electrocardiogram (ECG), or laboratory parameters were observed between combination and monotherapy groups, although the incidence of constipation was slightly higher with combination therapy and appeared to be dose related. The data from this study suggested that combination treatment may provide an attractive option to maximise efficacy and minimise AEs, resulting in two combinations (S5 + M25 and S5 + M50) being investigated further in phase III studies.

**Table 1 – Clinical trials from sponsored studies conducted to explore the efficacy, safety, and tolerability of mirabegron as add-on and/or combination therapy with antimuscarinics in patients with overactive bladder (primary data).**

| | SYMPHONY [16] | SYNERGY [22] | BESIDE [17] | SYNERGY II [20] | MILAI study [30] |
|---|---|---|---|---|---|
| National clinical trial no. | NCT01340027 | NCT01972841 | NCT01908829 | NCT02045862 | NCT01745094 |
| Phase | II | III | IIIb | III | IV |
| Sites/countries | 141 sites in 20 European countries | 435 sites in 42 countries | Eastern Europe, Western Europe, North America, Middle East, and Asia (number of sites/countries not specified) | 251 sites in 32 countries | 29 sites in Japan |
| Patients randomised (*N*) | 1307 | 3527 | 2174 | 1829 | 223 |
| Treatment duration and study design | 12 wk | 12 wk | 12 wk | 12 mo | 16 wk |
| | Randomised, double-blind treatment | Randomised, double-blind treatment | Randomised, double-blind treatment | Randomised, double-blind, active controlled treatment | Open-label study |
| Run-in/washout period (wk) | 2 (single-blind placebo run in) | 4 (single-blind placebo run in) | 6 (2, no treatment; 4, single-blind solifenacin run in) | 2 (single-blind placebo run in) | 0 |
| Treatment groups | Placebo | Placebo, M25, M50, S5, S5 + M25, S5 + M50 | S5, S10, and S5 + M25 increased to S5 + M50 after 4 wk | M50, S5, S5 + M50 | S2.5 + M25 for 8 wk increased to S2.5 + M50 for 8 wk if required |
| | 6 combination groups: S2.5/5/10 + M25/50 | | | | S5 + M25 for 8 wk increased to S5 + M50 for 8 wk if required |
| | 5 monotherapy groups: S2.5/5/10, M25/50 | | | | |
| Treatment phase duration | 12 wk | 12 wk | 12 wk | 12 mo | 16 wk |
| Primary objectives | To evaluate the efficacy and safety of combination therapy (S2.5 + M50, S5 + M25, and S5 + M50) vs monotherapy (S5) in patients with OAB | To evaluate the efficacy and safety of combined therapy (S5 + M25 and S5 + M50) vs each monotherapy in patients with OAB + incontinence | To evaluate efficacy, safety and tolerability of S5 + M25 increasing to S5 + M50 vs S5 or S10 after 4 wk of S5 in patients with OAB + incontinence | To evaluate the long-term safety and efficacy of S5 + M50 vs monotherapy in patients with OAB + incontinence | To evaluate the safety of mirabegron as "add-on" therapy to S2.5 or S5 in patients with OAB |
| Key findings | Combination therapy provided significant improvements in MVV and urgency (all groups), micturition frequency (S5 + M50, S10 + M25, S10 + M50), and IE (S5 + M25) vs S5 and placebo | Combination therapy (S5 + M25 and S5 + M50) provided consistent improvements in efficacy vs S5, M25, or M50 | Statistically significant improvement in UI/d (primary endpoint), mean daily micturitions and 3-d UI episodes (key secondary endpoints), micturition frequency, and patients becoming dry at EoT for S5 + M50 vs S5 | Combination therapy was well tolerated over 12 mo and led to efficacy improvements over each monotherapy | Addition of mirabegron to S2.5 or S5 was well tolerated, and resulted in a significant improvement in clinical outcomes and PRO scores |
| | | | Combination was noninferior to S10 for both key secondary endpoints and superior to S10 for reduction in micturition frequency | | |

EoT = end of treatment; M25 = mirabegron 25 mg; M50 = mirabegron 50 mg; MVV = mean volume voided; *N* = number of patients with OAB; OAB = overactive bladder; PRO = patient-reported outcome; S10 = solifenacin 10 mg; S2.5 = solifenacin 2.5 mg; S5 = solifenacin 5 mg; UI = urinary incontinence.

### 3.3. *Phase III trials of mirabegron plus solifenacin*

Three phase III/IIIb trials, SYNERGY (12 wk; *N* = 3527) [22], BESIDE (12 wk; *N* = 2174) [17], and SYNERGY II (12 mo; *N* = 1829) [20] primarily investigated the efficacy and safety of combination/add-on therapy (S + M) versus monotherapy in patients with OAB and incontinence (Tables 1 and 2). Patients included in BESIDE responded inadequately to 4-wk S5 treatment and received mirabegron as add-on therapy, whereas those included in SYNERGY or SYNERGY II could be treatment naïve. The active treatment groups between the three studies included the combination regimens, S5 + M25 and/or S5 + M50, and monotherapy (S5, S10, M25, and/or M50). Approximately 80% of patients included in each study were female, approximately 80–95% were white, and the mean age was between 57 and 61 yr

**Table 2 – Clinical trials from independent studies conducted to explore the efficacy, safety, and tolerability of mirabegron as add-on and/or combination therapy with antimuscarinics in patients with overactive bladder (primary data).**

| | Kosilov et al. [24] | Shin et al. [27] |
|---|---|---|
| Country | Russia | Korea |
| Randomised patients (*N*) | 239 | 30 |
| Duration and study design | Randomised placebo-controlled study of M50, S10, and S10 + M50 | M50 (4 wk), M50 + P10 (add-on 8 wk) |
| | Follow-up: 3 mo | Follow-up: not mentioned |
| Treatment phase duration (wk) | 6 | 8 |
| Primary objectives | Comparison of effectiveness and safety of S10 and M50 monotherapy vs combination in patients with OAB + severe incontinence, aged >65 yr | To assess the PRO and efficacy of add-on low-dose P10 therapy in OAB patients with suboptimal response to 4-wk treatment with M50 |
| Key finding | Statistically significant improvements from baseline to EoT in clinical and urodynamic parameters observed for combination therapy | Improvements in clinical outcomes and PRO scores were observed after 8 wk of add-on therapy |

EoT = end of treatment; M50 = mirabegron 50 mg; MVV = mean volume voided; *N* = number of patients with OAB; OAB = overactive bladder; P10 = propiverine HCl, 10 mg; PRO = patient-reported outcome; S10 = solifenacin 10 mg.

across the treatment groups in each trial (Supplementary Table S4). Groups were well balanced with respect to age, sex, and race in the three studies.

*3.3.1. Efficacy outcomes for mirabegron-based combination therapy*

In SYNERGY, combination therapy (S5 + M25 and S5 + M50) provided consistent improvements from baseline to EoT in efficacy versus respective monotherapies (S5, M25, or M50) across most of the outcome parameters, with effect sizes generally being consistent with an additive effect [22]. The primary objective was not met by a small margin for one of the coprimary endpoints (change from baseline to EoT in the mean number of UI episodes/24 h, $p = 0.052$), but the nominal $p$ value for the other coprimary endpoint (change from baseline to EoT in the mean number of micturitions/24 h) was $p < 0.05$; continuous variables for coprimary outcomes are reported in Tables 3 and 4. In secondary analyses, all active treatment groups had greater improvements in the mean number of UI episodes/24 h versus placebo. For micturitions/24 h, the mean adjusted change from baseline to EoT was greater in the combination therapy groups versus the monotherapy and placebo groups. The differences were evident from week 4 onwards, and the two combination therapies showed the largest improvements at all time points (Fig. 2) versus monotherapies. Similarly, improvements in the secondary efficacy parameters (MVV/micturition, urgency UI [UUI] episodes, urgency episodes, and nocturia) at EoT were greater with combination therapy than with monotherapy (with the exception of S5 + M25 for nocturia), and the effect size appeared to be additive. Responder analyses showed odds ratios in favour of combination therapy versus monotherapies for the proportion of patients with zero UI episodes and those achieving micturition frequency normalisation (Supplementary Tables 5 and 6).

A predefined subgroup analysis found that those who had received previous OAB treatment showed a much larger effect size than treatment-naïve patients in MVV/micturition and UUI episodes/24 h for combination therapy versus monotherapy; this was especially the case compared with S5 [22]. For S5 + M50 versus S5, the effect size for MVV/micturition was 17.13 ml for previously treated patients versus 1.48 ml in treatment-naïve patients, and the corresponding values were 7.46 and 0.59 ml for S5 + M25 versus S5. Similarly, the effect size for S5 + M50 versus S5 for UUI episodes/24 h was −0.43 for previously treated patients and −0.06 for naïve patients; the corresponding values for S5 + M25 were −0.53 versus 0.02 episodes/24 h.

BESIDE met its objective demonstrating superiority for S5 + M50 over S5, as evident by the adjusted change from baseline to EoT in the primary efficacy endpoint (the mean number of UI episodes/24 h; Table 3), which was significantly greater with combination therapy than with S5 (−1.80 vs −1.53, $p = 0.001$) [17]. Significantly greater improvements with S5 + M50 versus S5 were also observed for MVV/micturition, UUI episodes/24 h, urgency episodes/24 h, and patients becoming dry at EoT. S5 + M50 was noninferior to S10 for both key secondary endpoints (the mean number of daily micturitions/24 h and the number of incontinence episodes noted in the 3-d diary at EoT) and superior to S10 only for reduction in micturition frequency.

A prespecified subanalysis according to age (<65 vs ≥65 yr and <75 vs ≥75 yr) was performed for BESIDE [19]. All three treatment groups, S5 + M25 (increased to 50 mg at week 4), S5, and S10, showed a reduction in the mean number of daily UI episodes at EoT, irrespective of age. The treatment differences between S5 + M50 and S5 were −0.24 (95% confidence interval [CI]: −0.49 to 0.01) episodes/24 h in the <65-yr age group and −0.32 (−0.69 to 0.06) episodes/24 h in the ≥65-yr age group. Similar treatment differences were observed in the <75-yr (−0.26, −0.48 to −0.04 episodes/24 h) and ≥75-yr (−0.26, −0.94 to 0.42 episodes/24 h) age groups. Treatment differences between S5 + M50 and S10 were slightly smaller versus S5, but remained consistent across the age-stratified cohorts. Differences for other efficacy parameters were also similar between age groups.

Efficacy results for SYNERGY II were in agreement with observations from SYNERGY and BESIDE, showing clinically meaningful and sustained improvements for up to 12 mo in clinical outcomes for S5 + M50 over each monotherapy [20] (Fig. 2C and 2D).

**Table 3 – Summary of the efficacy data reported for the phase III trials of mirabegron plus solifenacin combination therapy, SYNERGY, BESIDE, and SYNERGY II.**

| | SYNERGY trial (*N* = 3527) [22] | | | | BESIDE trial (*N* = 2174) [17] | | | SYNERGY II trial (*N* = 1829) [20] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatment duration | 12 wk (plus 4-wk run-in and 2-wk run-out periods) | | | | 12 wk following a 4-wk run-in period | | | 12 mo | | | |
| Efficacy parameters | UI episodes/ 24 h, mean[a] | Micturitions/ 24 h[b], mean | Volume voided/ micturition (ml), mean[a] | Patients with zero UI episodes, *n* (%) | UI episodes/ 24 h, mean[a] | Volume voided/ micturition (ml), mean (SE) | Patients with zero UI episodes, *n* (%) | UI episodes/ 24 h, mean (SE) | Micturitions/ 24 h[b], mean (SE) | Volume voided/ micturition (ml), mean (SE) | Patients with zero UI episodes, *n* (%) |
| | Change from BL | Change from BL | Change from BL | – | Change from BL | Change from BL | – | Change from BL | Change from BL | Change from BL | – |
| Placebo | −1.34 | −1.64 | 8.44 | 155 (37.6) | – | – | – | – | – | – | – |
| M25 | −1.70 | −2.00 | 13.32 | 166 (40.6) | – | – | – | – | – | – | – |
| M50 | −1.76 | −2.03 | 21.99 | 188 (46.3) | – | – | – | −1.6 (0.1) | −2.1 (0.1) | 21.8 (3.1) | 144 (47.8) |
| S5 | −1.79 | −2.20 | 30.99 | 177 (42.9) | −1.53 | 16.52 (1.97) | 267 (37.9) | −1.9 (0.1) | −2.2 (0.1) | 24.9 (3.1) | 158 (53.2) |
| S10 | – | – | – | – | −1.67 | 20.30 (1.97) | 280 (40.2) | – | – | – | – |
| C1 (S5 + M25) | −2.04 | −2.49 | 34.84 | 417 (50.7) | – | – | – | – | – | – | – |
| C2 (S5 + M50) | −1.98 | −2.59 | 39.73 | 426 (52.2) | −1.80 | 28.05 (1.97) | 325 (46.0) | −2.0 (0.1) | −2.6 (0.1) | 37.7 (1.6) | 696 (58.8) |
| C2 vs S5 | $p = 0.033$[c] | $p = 0.006$[c] | $p = 0.005$[c] | $p = 0.009$[d] | $p = 0.001$[c] | $p < 0.001$[c] | $p = 0.001$[c] | $p = 0.002$[c] | $p = 0.004$[c] | $p < 0.001$[c] | $p = 0.080$[d] |
| C2 vs S10 | – | – | – | – | $p = 0.008$ | $p = 0.005$ | $p = 0.033$ | – | – | – | – |
| C2 vs M50 | $p = 0.052$ | $p < 0.001$ | $p < 0.001$ | $p = 0.023$[d] | – | – | – | $p < 0.001$ | $p < 0.001$ | $p < 0.001$ | $p < 0.001$[d] |

BL = baseline; C1 = combination 1—S5 + M25; C2 = combination 2—S5 + M50; M25 = mirabegron 25 mg; M50 = mirabegron 50 mg; *N* = total number of patients with OAB symptoms; OAB = overactive bladder; S10 = solifenacin 10 mg; S5 = solifenacin 5 mg; SE = standard error; UI = urinary incontinence.

[a] Presented as a bar chart in original publication; values for mean specified on the chart but error bars provided only graphically.

[b] In BESIDE, the data for micturitions/24 h were available at baseline only: S5 = 8.90, S10 = 8.96, C2 = 9.12.

[c] *p* value for difference (combination vs monotherapy).

[d] *p* value from logistic regression model.

**Table 4 – Summary of HRQoL outcomes for phase III trials of mirabegron plus solifenacin combination therapy, SYNERGY, BESIDE, and SYNERGY II[a].**

| HRQoL parameters | SYNERGY trial ($N = 3527$) [26] | | | | | BESIDE trial ($N = 2174$) [17,21] | | | | | | SYNERGY II trial ($N = 1829$) [20] | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | OAB-q symptom bother score | OAB-q HRQoL total score | PPBC score | TS-VAS | PGIC general health, very much improved (%) | OAB-q symptom bother score | OAB-q HRQoL total score | PPBC score | Bladder symptoms very much/much improvement at EoT (%) | PGIC general health, very much/much improved (%) | CGIC bladder symptoms, very much/much improved (%) | OAB-q symptom bother score | OAB-q HRQoL total score | TS-VAS |
| | Change from BL[b] | Change from BL[b] | Change from BL[b] | Change from BL[b] | – | Change from BL[b] | Change from BL[b] | Change from BL[b] | – | – | – | Change from BL[b] | Change from BL[b] | Change from BL[b] |
| Placebo | −19.5 | 15.4 | −0.9 | 1.4 | 8 | – | – | – | – | – | – | – | – | – |
| M25 | −23.9 | 18.9 | −1.2 | 2.2 | 14 | – | – | – | – | – | – | – | – | – |
| M50 | −26.1 | 21.0 | −1.3 | 2.2 | 15 | – | – | – | – | – | – | −22.0 | 16.6 | 2.2 |
| S5 | −26.4 | 20.2 | −1.3 | 2.3 | 14 | −21.93 | 17.63 | −1.2 | 63.4 | 51.9 | 64.8 | −24.9 | 18.5 | 2.2 |
| S10 | – | – | – | – | – | −23.59 | 17.40 | −1.3 | 67.3 | 52.0 | 69.0 | – | – | – |
| C1 (S5 + M25) | −31.1 | 24.0 | −1.5 | 2.5 | 20 | | | – | – | – | – | – | – | – |
| C2 (S5 + M50) | −32.2 | 24.3 | −1.7 | 2.6 | 27 | −26.89 | 20.78 | −1.5 | 73.9 | 58.8 | 74.1 | −29.5 | 21.3 | 2.7 |
| C2 vs S5 | $p < 0.001$ | $p < 0.001$ | $p < 0.001$ | $p = 0.05$ | NR | −4.96; $p < 0.001$ | 3.15; $p = 0.001$ | $p < 0.001$ | $p < 0.01$ | $p = 0.01$ | $p < 0.01$ | $p < 0.001$ | $p = 0.01$ | $p < 0.001$ |
| C2 vs S10 | – | – | – | – | – | −3.30; $p = 0.001$ | 3.38; $p < 0.001$ | $p = 0.004$ | $p = 0.01$ | $p = 0.01$ | $p = 0.03$ | – | – | – |
| C1 vs M25 | $p < 0.001$ | $p < 0.001$ | $p < 0.001$ | $p = 0.008$ | NR | | | – | – | – | – | – | – | – |
| C2 vs M50 | $p < 0.001$ | $p = 0.002$ | $p < 0.001$ | $p = 0.007$ | NR | | | – | – | – | – | $p < 0.001$ | $p < 0.001$ | $p < 0.001$ |

BL = baseline; C1 = combination 1—S5 + M25; C2 = combination 2—S5 + M50; CGIC = Clinician Global Impression of Change; EoT = end of treatment; EQ-5D-5 L = European Quality of Life-5 Dimensions; HRQoL = health-related quality of life; M25 = mirabegron 25 mg; M50 = mirabegron 50 mg; NR = not reported; OAB-5D = Overactive Bladder-5 Dimensions; OAB-q = Overactive Bladder Questionnaire; PGIC = Patient Global Impression of Change; PPBC = patient perception of bladder condition; S5 = solifenacin 5 mg; S10 = solifenacin 10 mg; TS-VAS = treatment satisfaction visual analogue scale.

[a] Improvement in symptoms from baseline indicated by a greater reduction in OAB-q symptom bother score and PPBC score, and greater increases in OAB-q HRQoL total score, TS-VAS, EQ-5D-5 L, and OAB-5D.

[b] Mean adjusted change from BL to EoT.

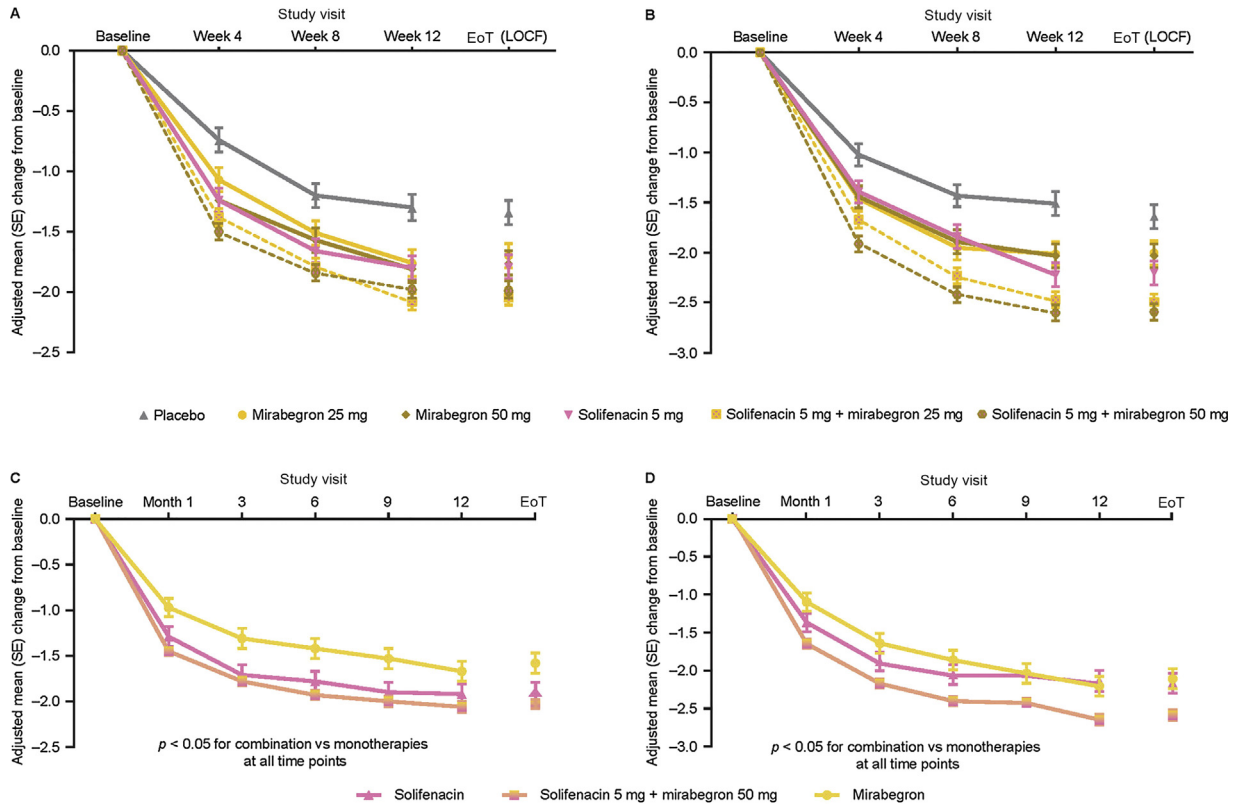


**Fig. 2 – Adjusted change from baseline in the mean number of UI episodes/24 h and micturitions/24 h during follow-up (A and B) for 12 wk in SYNERGY [22] and (C and D) 12 mo in SYNERGY II [20]. EoT = end of treatment; LOCF = last observation carried forward; SE = standard error; UI = urinary incontinence. Reprinted from 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). Eur Urol 2018;74:501-9, with permission from Elsevier.**

### 3.3.2. *HRQoL for mirabegron-based combination therapy*

HRQoL was evaluated in all three phase III studies using a range of HRQoL tools. Results from the three studies consistently showed a similar or greater improvement in HRQoL for combination therapy versus mirabegron or solifenacin monotherapy (Table 4 and Supplementary Table S3). The minimally important difference is 10 for all Overactive Bladder Questionnaire (OAB-q) subscales [33]. In SYNERGY, both combinations (S5 + M50 and S5 + M25) showed similar or greater improvements in all parameters versus monotherapy (S5, M25, and M50) [26]. In BESIDE, statistically significant ($p < 0.05$) improvements over baseline with S5 + M50 versus S5 or S10 were seen in all measures assessed [17,21]. The mean adjusted differences were −4.96 and −3.30 in symptom bother score ($p \leq 0.001$) and 3.15 and 3.38 in total HRQoL ($p \leq 0.001$) for the combination versus S5 and S10 groups, respectively. At EoT, the OAB-5 Dimension score, Clinician Global Impression of Change bladder symptoms score and Patient Global Impression of Change general health score in the S5 + M50 combination group were significantly improved compared with the S5 and S10 groups ($p \leq 0.01$). Improvements in the PRO measures assessed in SYNERGY II over the 12-mo period were greater with combination therapy (S5 + M50) versus M50 or S5 [20].

### 3.3.3. *Safety outcomes for mirabegron-based combination therapy*

Most TEAEs in all treatment groups in SYNERGY [22], BESIDE [17], and the long-term safety study SYNERGY II [20] were mild or moderate in severity. The incidences of dry mouth, constipation, and UTIs were <10% in all studies across all regimens (Table 5), and there were no notable between-group differences in vital signs, ECG parameters, or PVR volume. In SYNERGY II, 47% of patients experienced one or more TEAEs across all groups. Urinary retention was reported slightly more frequently in the combined therapy groups (0.9–1.2%) than in the monotherapy (0.7% S5 only) and placebo (0%) groups in SYNERGY, with a majority not requiring catheterisation. In BESIDE, urinary retention was reported in 0.3% of patients receiving combination therapy versus 0.1–0.7% of those receiving monotherapy (no catheterisation required), and in 0.7% and 0.3% of patients in the combination and monotherapy groups, respectively, of SYNERGY II.

Cardiovascular (CV) AEs, vital signs, and ECG data were collected prospectively for 3398 patients in SYNERGY [29]. There were no clinically meaningful differences in change from baseline in ECG parameters or QT interval corrected for Fridericia's correction formula (QTcF) prolongation between the monotherapies and placebo, and between monotherapy and combination therapy. Increased BP was reported in 62 (1.8%) patients, and the frequencies

**Table 5 – Summary of key safety data for the phase III trials of mirabegron plus solifenacin combination therapy, SYNERGY, BESIDE, and SYNERGY (safety analysis sets) II.**

| Clinical trial | SYNERGY ($N$ = 3398) [22] | | | | | | BESIDE ($N$ = 2172) [17] | | | | | | SYNERGY II ($N$ = 1814) [20] [a] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatment duration | 12 wk (plus 4-wk run-in and 2-wk run-out periods) | | | | | | 12 wk following a 4-wk run-in period | | | | | | 12 mo | | | |
| | TEAE | | | PVR volume (ml) | | | TEAE | | | PVR volume (ml) | | | TEAE | | | |
| | $n$ | DM, $n$ (%) | Cons, $n$ (%) | UTI, $n$ (%) | $n$ | Mean (SD) change from BL to EoT | $n$ | DM, $n$ (%) | Cons, $n$ (%) | UTI, $n$ (%) | $n$ | Mean (SD) change from BL to EoT | $n$ | DM, $n$ (%) | Cons, $n$ (%) | UTI, $n$ (%) |
| Placebo | 429 | 8 (1.9) | 6 (1.4) | 21 (4.9) | 410 | −1.0 (29.4) | – | – | – | – | | | – | – | – | – |
| M25 | 423 | 17 (4.0) | 6 (1.4) | 18 (4.3) | 401 | 0.7 (29.1) | – | – | – | – | | | – | – | – | – |
| M50 | 422 | 14 (3.3) | 11 (2.6) | 16 (3.8) | 404 | −0.8 (30.0) | – | – | – | – | | | 305 | 12 (3.9) | 3 (1.0) | 11 (3.6) |
| S5 | 423 | 25 (5.9) | 6 (1.4) | 21 (5.0) | 414 | 4.8 (33.3) | 728 | 41 (5.6) | 22 (3.0) | 16 (2.2) | 713 | 3.0 (43.5) | 303 | 18 (5.9) | 7 (2.3) | 12 (4.0) |
| S10 | – | – | – | – | – | – | 719 | 68 (9.5) | 34 (4.7) | 20 (2.8) | 707 | 7.4 (54.1) | – | – | – | – |
| C1 (S5 + M25) | 853 | 74 (8.7) | 38 (4.5) | 60 (7.0) | 821 | 9.0 (55.0) | – | – | – | – | | | – | – | – | – |
| C2 (S5 + M50) | 848 | 61 (7.2) | 31 (3.7) | 44 (5.2) | 815 | 11.0 (54.9) | 725 | 43 (5.9) | 33 (4.6) | 17 (2.3) | 706 | 5.5 (51.6) | 1206 | 74 (6.1) | 40 (3.3) | 41 (3.4) |

BL = baseline; C1 = combination 1—S5 + M25; C2 = combination 2—S5 + M50; Cons = constipation; DM = dry mouth; EoT = end of treatment; M25 = mirabegron 25 mg; M50 = mirabegron 50 mg; $N$ = number of patients assessed; PVR = postvoid residual; S10 = solifenacin 10 mg; S5 = solifenacin 5 mg; SD = standard deviation; TEAE = treatment-emergent adverse event; UTI = urinary tract infection.
[a] PVR volume reported in text only: "PVR volume was slightly higher in the combination group compared with both monotherapy groups at most visits".

were similar across combination and mirabegron treatment groups. There were nominally more reports of increased BP in the S5 group (2.6%). Other CV disorders were marginally more frequent in the combination groups. Treatment-emergent hypertension ranged from 0.7% in the M25 group to 1.9% in the S5 group compared with 1.2% in the placebo group. Overall, combination therapies showed similar rates of CV AEs versus monotherapy.

A substudy of SYNERGY assessed BP and heart rate using ambulatory BP monitoring in 715 patients [28]. Five patients experienced clinically significant increases in systolic BP (SBP): one each in the M25 (1.4%) and M50 (1.3%) groups, two (2.6%) in the S5 group, and one (0.7%) in the S5 + M25 group. Two patients, one each (1.3%) in the S5 and placebo groups, experienced clinically significant increases in diastolic BP (DBP). Only one patient (1.3%) in the M50 group experienced a potentially clinically significant increase in heart rate.

CV safety outcomes reported from BESIDE were consistent with those reported from SYNERGY [18]. The frequency of hypertension, tachycardia, and ECG-QT prolongation was low and similar across treatment groups. The adjusted mean change from baseline to EoT in SBP, DBP, and pulse rate was similar between treatment groups, with the exception of a mean treatment difference of approximately 1 mmHg in SBP between the combination and S5 groups. The latter reflected the fact that SBP was unchanged during combination treatment and decreased during treatment with S5. The only difference between the therapies was in change from baseline in QTcF interval, which was higher with S10 (3.30 ms) versus combination (0.49 ms) and S5 (0.77 ms). The results indicated that a combination of mirabegron and solifenacin does not have any additive adverse effect on the CV system. None of the observed changes were clinically significant.

### 3.4. *Other studies of mirabegron plus antimuscarinic therapy*

Three additional studies evaluated the clinical efficacy and safety of combinations of mirabegron plus antimuscarinic therapy in patients with moderate-to-severe OAB (Tables 1 and 2) [24,27,30].

Kosilov et al. [24] reported efficacy outcomes for M50, S10, and S10 + M50 in a randomised placebo-controlled study in 239 treatment-experienced patients with OAB and incontinence, aged >65 yr, who received therapy for 6 wk. In the S10 + M50 group, the urodynamic results were significantly ($p < 0.05$) different from the values in two monotherapy groups. OAB-q scores improved marginally in the S10, M50, and placebo groups, but showed much larger improvement with combination therapy. The incidence of AEs, including increases in BP, dry mouth, heart rate, and dizziness, did not differ significantly for combination therapy versus monotherapy.

A multicentre, open-label, phase IV study conducted in Japan [30] evaluated the safety (primary endpoint) and efficacy of mirabegron (25 mg once daily for 16 wk, with an optional increase to 50 mg at week 8) as an "add-on" therapy in adults with OAB ($n$ = 223) treated with solifenacin at a stable dose of 2.5 or 5 mg once daily for at least 4 wk.

TEAEs, which were generally mild or moderate in severity, were observed in 23.3% of patients, the most common being constipation (6.3%) with no apparent dose-related changes. An increase in the QTcF interval (>30 and ≤60 ms) from baseline to EoT was seen in three patients (1.4%), which was not considered to be clinically significant. There were no notable changes from baseline in vital signs, ECG, laboratory tests, and mean PVR volume in any group. At EoT, efficacy evaluation indicated that the addition of mirabegron resulted in a significant improvement in clinical outcomes and PRO scores in all treatment groups ($p < 0.05$).

Shin et al. [27] assessed the efficacy of low-dose add-on antimuscarinic therapy (propiverine, 10 mg for 8 wk) in a small group of patients with OAB ($n = 30$; mean age, 62.3 yr) who had a suboptimal response (patient perception of bladder condition score ≥4) to 4 wk of treatment with M50 monotherapy. Improvements in PRO scores (primary endpoint) and clinical outcomes were observed after 8 wk of add-on therapy. Three patients reported mild dry mouth, but there were no reports of acute urinary retention.

### 3.5. Efficacy and safety of dual antimuscarinic therapy (trospium plus solifenacin)

Five publications by Kosilov et al. [10–12,23,25] reported the efficacy and safety of dual antimuscarinic therapy, trospium plus solifenacin, in patients aged ≥65 yr with moderate-to-severe OAB symptoms. The first of these publications [23] reported that trospium 60 mg/d (T60) + solifenacin 40 mg/d (unlicensed dose; S40) given for 1 mo provided effective maintenance therapy in women with OAB who had already responded to the same regimen administered for 6 wk as initial therapy ($n = 229$; mean age 66.3 yr). After 6 and 12 mo, improvements from baseline in daily UI events, urgency episodes/d, number of micturitions/d, and MVV/micturition were statistically significant in patients receiving T60 + S40. In addition, significant improvement in quality of life was reported in 78% of patients due to regression of OAB symptoms by the end of the follow-up period. A follow-up study [11] investigated lower doses of trospium—30 mg/d (T30) + S10 and trospium 15 mg/d (T15) + S5—administered for 2 mo and showed similar decreases in the frequency of UI episodes/d with both doses in patients with moderate OAB symptoms ($n = 177$; mean age 69.4 yr). A third study compared the efficacy of T60 + solifenacin 20 mg/d (unlicensed dose; S20) or T30 + S10 given as three 8-wk cycles separated by an 8-wk interval and that of T30 + S10 given continuously for 1 yr in patients with severe OAB ($n = 341$; mean age 69.9 yr) [25]. While all three regimens provided effective control for up to 12 mo and were well tolerated, compliance was higher for the cyclic regimens. In a further study, a one-cycle regimen of T60 + S20 provided prolonged symptom control for up to 6 mo in patients with moderate symptoms, whereas a two-cycle regimen was required to provide sustained symptom control in patients with severe symptoms ($n = 313$; mean age 68.6 yr) [10]. The fifth study ($n = 327$; median age 69.1 yr) [12] reported that a 6-wk course of T30 + S10 or T60 + S20 provided effective control in patients with moderate or severe OAB symptoms, respectively, who had previously experienced unsuccessful antimuscarinic treatment.

### 3.6. Discussion

The results of this rapid evidence assessment highlight a substantial body of evidence supporting the efficacy of mirabegron plus solifenacin combination/add-on therapy for the treatment of OAB versus either agent as monotherapy, as demonstrated in three phase III studies (SYNERGY [22], BESIDE [17], and SYNERGY II [20]). Both 12-wk trials (SYNERGY and BESIDE) consistently reported numerical improvements in clinical outcomes for combination therapy versus monotherapy, most of which were statistically significant. In addition, the greater improvements in clinical outcomes for combination therapy versus monotherapy were found to be sustained over 12 mo of therapy in SYNERGY II. Improvements in HRQoL measures over the 12 wk of treatment in SYNERGY and BESIDE were also similar to or greater than that for combination therapy versus monotherapy. These improvements in symptoms were achieved without significant safety concerns or clinically meaningful increases in the incidence of AEs. Results from these three studies are supported by results from three smaller studies, two of which investigated either mirabegron as add-on therapy to solifenacin [30] or another antimuscarinic therapy, propiverine, as add-on therapy to mirabegron [27]. These results indicate that combining mirabegron with a low-dose antimuscarinic provides improved efficacy without adding to the burden of typical antimuscarinic-related side effects that may accompany high-dose treatment. The evidence confirms that this regimen can provide a valuable treatment option for patients with OAB who do not achieve adequate response to antimuscarinic monotherapy; it may also limit the anticholinergic burden for elderly patients with OAB. Recently, the MILAI II study [34] provided supporting evidence that add-on therapy with an antimuscarinic drug (solifenacin, propiverine, imidafenacin, or tolterodine) was well tolerated and effective in patients with residual OAB symptoms following 6 wk of treatment with mirabegron.

Approximately 50% of patients included in SYNERGY and SYNERGY II, and 68% of patients in BESIDE had received OAB medication prior to entering the trials. In SYNERGY, treatment benefit for combination therapy versus monotherapy was numerically greater in patients who had received prior therapy [22], suggesting that the benefits of combination therapy are not limited to patients who are treatment naïve. The efficacy data reported for BESIDE where patients who remained incontinent after 4 wk of S5 treatment received mirabegron add-on therapy further suggest that the benefits of mirabegron combination therapy are seen in patients who had previously received antimuscarinic therapy. In all three studies, clinical efficacy of the combination seemed to be additive at the tested doses.

Importantly, improvements in efficacy with combination therapy over monotherapy appear to be similar between

older (>65 or >75 yr) and younger age groups, according to data from BESIDE [17]. Furthermore, the incidence of AEs was generally similar across treatment groups and age, although the incidence of overall TEAEs was numerically higher in the S10 group, particularly in the older age cohorts (>65 and >75 yr). These data suggest that combination therapy is well tolerated in elderly patients and may offer an advantage over higher doses of antimuscarinic monotherapy. Although improvements in the monotherapy subgroup may be considered low, they fall well within the 95% CI of the main effect in the overall population. Moreover, the study was not designed to assess treatment effect in treatment-naïve patients, so indeed robust evidence has not been provided.

In agreement with the findings from these studies, treatment guidelines for the management of OAB recommend combination therapy involving mirabegron and an antimuscarinic agent as an option for patients who do not achieve a satisfactory response to monotherapy. For example, the AUA 2015 guidelines suggest that combination therapy should be used when monotherapy fails or in patients with refractory symptoms [8]. EAU 2019 guidelines recommend that "if an antimuscarinic treatment proves ineffective, consider dose escalation or offering an alternative antimuscarinic formulation or mirabegron or a combination" and note that patients inadequately treated with S5 may benefit more from the addition of mirabegron than solifenacin dose escalation [5]. Furthermore, following the publication of the SYNERGY and BESIDE trial results, updated AUA guidelines (April 2019) recommend the use of combination treatment (antimuscarinic and β3-adrenoreceptor agonist) in patients refractory to either monotherapy [35]. This, in addition to EAU treatment guidelines already recommending combination treatment for OAB, provides clear guidance on combination treatment use.

Results from the publications identified in this review suggest that M50 + S5 is an effective combination for patients with OAB for whom monotherapy is inadequate and may thus be an alternative to dose escalation of antimuscarinic agents. Achieving effective control with pharmacotherapy also obviates the need for escalation to more invasive therapies such as neuromodulation and botulinum toxin injections, and is beneficial to patients across all age groups.

The review also identified five studies investigating combination therapy consisting of two antimuscarinic drugs [10–12,23,25]. Although these studies were generally small and, in some cases, involved unlicensed doses, they suggest that dual antimuscarinic therapy may be effective in elderly patients with moderate-to-severe symptoms. However, as only one small study has reported the efficacy of two antimuscarinics (including the use of an unlicensed dose) in patients refractory to initial antimuscarinic treatment, it is not possible to conclude whether such a combination is effective or safe in the long term, as such combination treatment cannot be recommended. Additional studies are, therefore, warranted to further investigate the effectiveness and long-term safety of this combination treatment. A phase IIb placebo-controlled study recently reported that once-daily vibegron 100 mg monotherapy was efficacious and well tolerated as monotherapy and in combination with tolterodine ER 4 mg, but with no additional benefits for combination therapy [36].

Although this is a robust and rigorous methodology, the shortened timelines for the rapid review may impact the overall scale and scope of the search, resulting in the possible omission of relevant studies. However, certain steps (such as the hand-searching references in previously published literature reviews) minimises this limitation [37]. A limitation of the findings of this review is that all the evidence for the efficacy and safety of mirabegron plus solifenacin comes from interventional clinical trials in which the patients may not be fully representative of patients in routine clinical practice, for example, with respect to age and comorbidities. No real-world studies were identified; such studies are likely to reflect clinical practice realities, such as medication discontinuation, more closely. However, all five sponsored trials were multicentre, and the findings of the two independent studies were consistent with those of the sponsored trials. Furthermore, the patient populations involved different races, patients with different degrees of symptom severity, and those having received different prior treatments. The evidence presented here was identified through the performance of a rigorous systematic literature search, and most (>70%) of the 21 identified publications were rated as being of moderate or high quality.

## 4. Conclusions

Evidence from this review indicates that the combination of mirabegron (50 mg) and solifenacin (5 mg) provides an effective and well-tolerated treatment option in adult patients with inadequate control of OAB symptoms on monotherapy as well as in treatment-naïve patients. Clinically meaningful improvements in symptoms were accompanied by gains in HRQoL, and both were found to be sustained through treatment for up to 12 mo. Combination therapy with an antimuscarinic plus mirabegron therefore seems to be a dependable option for replacing monotherapy in patients with persistent OAB symptoms. Although further studies are required concerning treatment with two antimuscarinics, limited evidence suggests that this option may be effective in patients with moderate-to-severe OAB symptoms, although no long-term safety data are currently available. Further studies may help characterise patients who could benefit from initiating combination therapy early in the course of their condition.

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*Study concept and design:* Stoelzel, van Maanen, Siddiqui, Rolland.

*Acquisition of data:* Rolland.

*Analysis and interpretation of data:* Gratzke, Chapple, Mueller, Robinson, Rolland, Staskin, Stoelzel, van Maanen, Siddiqui.

*Drafting of the manuscript:* Gratzke, Chapple, Mueller, Robinson, Rolland, Staskin, Stoelzel, van Maanen, Siddiqui.

*Critical revision of the manuscript for important intellectual content:* Gratzke, Chapple, Mueller, Robinson, Rolland, Staskin, Stoelzel, van Maanen, Siddiqui.
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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eururo.2019.07.010.

## References

[1] Drake MJ. Do we need a new definition of the overactive bladder syndrome? ICI-RS 2013. Neurourol Urodyn 2014;33:622–4.
[2] Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the International Continence Society. Urology 2003;61:37–49.
[3] Eapen RS, Radomski SB. Review of the epidemiology of overactive bladder. Res Rep Urol 2016;8:71–6.
[4] 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;108:1132–8.
[5] Nambiar AK, Bosch R, Cruz F, et al. EAU guidelines on assessment and nonsurgical management of urinary incontinence. Eur Urol 2018;73:596–609.
[6] Deeks ED. Mirabegron: a review in overactive bladder syndrome. Drugs 2018;78:833–44.
[7] Yoshida M, Kato D, Nishimura T, Van Schyndle J, Uno S, Kimura T. Anticholinergic burden in the Japanese elderly population: use of antimuscarinic medications for overactive bladder patients. Int J Urol 2018;25:855–62.
[8] 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;193:1572–80.
[9] Corcos J, Przydacz M, Campeau L, et al. CUA guideline on adult overactive bladder. Can Urol Assoc J 2017;11:E142–73.
[10] Kosilov K, Loparev S, Iwanowskaya M, Kosilova L. Effectiveness of combined high-dosed trospium and solifenacin depending on severity of OAB symptoms in elderly men and women under cyclic therapy. Cent Eur J Urol 2014;67:43–8.
[11] Kosilov KV, Loparev SA, Ivanovskaya MA, Kosilova LV. Comparative effectiveness of combined low- and standard-dose trospium and solifenacin for moderate overactive bladder symptoms in elderly men and women. Urol Int 2014;93:470–3.
[12] Kosilov KV, Loparev SA, Ivanovskaya MA, Kosilova LV. Influence of different doses of trospium and solifenacin on manageability of OAB symptoms with different severity in elderly men and women. J Clin Urol 2016;9:180–8.
[13] Crawford C, Boyd C, Jain S, Khorsan R, Jonas W. Rapid Evidence Assessment of the Literature (REAL((c))): streamlining the systematic review process and creating utility for evidence-based health care. BMC Res Notes 2015;8:631.
[14] Guyatt G, Oxman AD, Sultan S, et al. GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes. J Clin Epidemiol 2013;66:151–7.
[15] Abrams P, Kelleher C, Staskin D, et al. Combination treatment with mirabegron and solifenacin in patients with overactive bladder: exploratory responder analyses of efficacy and evaluation of patient-reported outcomes from a randomized, double-blind, factorial, dose-ranging, phase II study (SYMPHONY). World J Urol 2017;35:827–38.
[16] 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;67:577–88.
[17] 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;70:136–45.
[18] Drake MJ, MacDiarmid S, Chapple CR, et al. Cardiovascular safety in refractory incontinent patients with overactive bladder receiving add-on mirabegron therapy to solifenacin (BESIDE). Int J Clin Pract 2017;71:e12944.
[19] Gibson W, MacDiarmid S, Huang M, et al. Treating overactive bladder in older patients with a combination of mirabegron and solifenacin: a prespecified analysis from the BESIDE study. Eur Urol Focus 2017;3:629–38.
[20] 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). Eur Urol 2018;74:501–9.
[21] Herdman M, Nazir J, Hakimi Z, et al. Assessing preference-based outcome measures for overactive bladder: an evaluation of patient-reported outcome data from the BESIDE clinical trial. Patient 2017;10:677–86.

[22] 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;120:562–75.
[23] Kosilov K, Loparev S, Ivanovskaya M, Kosilova L. Maintenance of the therapeutic effect of two high-dosage antimuscarinics in the management of overactive bladder in elderly women. Int Neurourol J 2013;17:191–6.
[24] Kosilov K, Loparev S, Ivanovskaya M, Kosilova L. A randomized, controlled trial of effectiveness and safety of management of OAB symptoms in elderly men and women with standard-dosed combination of solifenacin and mirabegron. Arch Gerontol Geriatr 2015;61:212–6.
[25] Kosilov KV, Loparev SA, Ivanovskaya MA, Kosilova LV. Randomized controlled trial of cyclic and continuous therapy with trospium and solifenacin combination for severe overactive bladder in elderly patients with regard to patient compliance. Ther Adv Urol 2014;6:215–23.
[26] Robinson D, Kelleher C, Staskin D, et al. Patient-reported outcomes from SYNERGY, a randomized, double-blind, multicenter study evaluating combinations of mirabegron and solifenacin compared with monotherapy and placebo in OAB patients. Neurourol Urodyn 2018;37:394–406.
[27] Shin JH, Kim A, Choo MS. Additional low-dose antimuscarinics can improve overactive bladder symptoms in patients with suboptimal response to beta 3 agonist monotherapy. Invest Clin Urol 2017;58:261–6.
[28] Weber MA, Chapple CR, Gratzke C, et al. A strategy utilizing ambulatory monitoring and home and clinic blood pressure measurements to optimize the safety evaluation of noncardiovascular drugs with potential for hemodynamic effects: a report from the SYNERGY trial. Blood Press Monit 2018;23:153–63.
[29] White WB, Chapple C, Gratzke C, et al. Cardiovascular safety of the β3-Adrenoceptor agonist mirabegron and the antimuscarinic agent solifenacin in the SYNERGY trial. J Clin Pharmacol 2018. http://dx.doi.org/10.1002/jcph.1107, [Epub ahead of print].
[30] Yamaguchi O, Kakizaki H, Homma Y, et al. 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;116:612–22.
[31] MacDiarmid S, Al-Shukri S, Barkin J, et al. Mirabegron as add-on treatment to solifenacin in patients with incontinent overactive bladder and an inadequate response to solifenacin monotherapy. Journal of Urology 2016;196:809–18.
[32] Gratzke C, van Maanen R, Chapple CR, et al. Long-term combination treatment with solifenacin and mirabegron is effective and well tolerated in patients with overactive bladder. J Urol 2017;197:e607.
[33] Coyne KS, Matza LS, Thompson CL, Kopp ZS, Khullar V. Determining the importance of change in the overactive bladder questionnaire. J Urol 2006;176:627–32, discussion 632.
[34] Yamaguchi O, Kakizaki H, Homma Y, et al. Long-term safety and efficacy of antimuscarinic add-on therapy in patients with overactive bladder who had a suboptimal response to mirabegron monotherapy: a multicenter, randomized study in Japan (MILAI II study). Int J Urol 2019;26:342–52.
[35] Lightner DJ, Gomelsky A, Souter L, Vasavada SP. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline amendment. J Urol 2019. http://dx.doi.org/10.1097/JU.0000000000000309, [Epub ahead of print].
[36] Mitcheson HD, Samanta S, Muldowney K, et al. Vibegron (RVT-901/MK-4618/KRP-114V) administered once daily as monotherapy or concomitantly with tolterodine in patients with an overactive bladder: a multicenter, phase IIb, randomized, double-blind, controlled trial. Eur Urol 2019;75:274–82.
[37] Collins A, Coughlin D, Miller J, Kirk S. The production of quick scoping reviews and rapid evidence assessments. A how to guide. UK: Joint Water Evidence Group; 2015.