



The Relative Efficacy and Safety of Mirabegron and OnabotulinumtoxinA in Patients With Overactive Bladder who Have Previously Been Managed With an Antimuscarinic: A Network Meta-analysis

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OBJECTIVE	To compare the efficacy and safety of mirabegron and onabotulinumtoxinA in the management of treatment-experienced patients with overactive bladder.
METHODS	The network meta-analysis was based on evidence from a systematic literature review of randomized controlled trials and a post-hoc analysis of treatment-experienced subpopulations from mirabegron studies.
RESULTS	Nineteen trials described in 21 publications were included.
CONCLUSION	Overall, compared to mirabegron, there was some evidence that onabotulinumtoxinA was associated with improved outcomes, including reductions in the number of micturitions in a 24-hour period, and the number of incontinence episodes. However, mirabegron was associated with a lower risk of urinary tract infections compared with onabotulinumtoxinA. UROLOGY 127: 1–8, 2019. © 2019 The Author(s). Published by Elsevier Inc.

Overactive bladder (OAB) is a common condition, with symptoms affecting up to 35.6% of men and women ≥ 40 years of age in the United States (US), and prevalence increasing with age.¹ Characterized by urinary urgency, with or without urinary incontinence, nocturia, and urinary frequency, OAB often negatively impacts sleep, mental health, and work productivity of affected individuals.²

Behavioral therapies and lifestyle changes are initial treatments for OAB; if such interventions insufficiently manage symptoms, pharmacotherapy may be prescribed. Although the American Urological Association

recommends that antimuscarinics and mirabegron, a $\beta 3$ -adrenoreceptor, as first-line pharmacotherapy options for OAB,³ there is evidence that in clinical practice mirabegron may only be offered after treatment failure with antimuscarinics.⁴ Furthermore, it has been recently suggested that onabotulinumtoxinA, currently a third-line treatment option, could offer benefits to patients with OAB prior to treatment with antimuscarinics or mirabegron.⁵

Although several clinical trials have directly compared mirabegron to antimuscarinics,^{6–8} there have been no head-to-head comparisons of mirabegron versus onabotulinumtoxinA.

In the absence of direct comparisons, network-meta analyses (NMAs) have been conducted comparing the efficacy of mirabegron and onabotulinumtoxinA for the treatment of OAB^{9,10}; however, these have not investigated the relative safety of onabotulinumtoxinA versus mirabegron, nor have they appropriately accounted for the inherent differences in trial patient populations. Mirabegron (and antimuscarinic) trials have typically included a mixed patient population of treatment-naïve and treatment-experienced patients, while onabotulinumtoxinA trials have included treatment-experienced patients with a longer disease history and greater symptom severity. Heterogeneity in patient populations may lead to

Disclosures

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important variability in treatment prognosis. Furthermore, with the availability of new evidence from clinical trials, results from previous NMAs may have become outdated.¹¹⁻¹⁷

The NMA presented in this paper builds upon the existing literature. The primary aim of this study was to compare the efficacy of mirabegron 50 mg and onabotulinumtoxinA in the management of treatment-experienced patients with OAB. Additionally, this study aimed to compare the safety profiles of mirabegron and onabotulinumtoxinA in this population.

METHODS

Evidence Identification

Search Strategy. To inform the NMA, a comprehensive systematic search of the published literature was conducted through a review of the Medline and Medline in-progress (OVID SP), EMBASE (OVID SP) (which includes the Cochrane Central Register of Controlled Trials [CENTRAL]), and PubMed databases. The search was not limited by country or geographic region; however, it was limited to English language publications. The study period was from January 1, 2005 to October 19, 2016, defined to capture all relevant studies including mirabegron or onabotulinumtoxinA, while ensuring a contemporary patient population for publications focusing on antimuscarinics. The search was guided by the population, interventions and/or comparators, outcomes, study design criteria (Supplementary Table 1). Studies eligible for inclusion were among adults (≥ 18 years) with OAB who have received at least one prior OAB pharmacotherapy (to be eligible for inclusion, at least 80% of the patient population described in the study was required to be treatment-experienced, or have endpoints reported for the subgroup of treatment-experienced patients) and included one or more treatments of interest. Although the search was not specific to the US, only treatments approved for use in the US and placebo were eligible. As such, mirabegron (25 or 50 mg), onabotulinumtoxinA (100 U), and any of the antimuscarinics most commonly used in the US to treat OAB, including darifenacin (7.5, 15 mg), fesoterodine (4, 8 mg), oxybutynin (transdermal patch: 3.9 mg; gel: 100 mg; syrup: 5 mg; tablet: 5, 10, 15 mg), solifenacin (5, 10 mg), tolterodine (1, 2, 4 mg) or trospium chloride (60 mg) or to no treatment and/or placebo were included. An *a priori* decision was made to include studies that compared two or more antimuscarinics or compared an antimuscarinic to a placebo, as they had the potential of contributing intermediate information to the network of evidence, for the comparison of mirabegron versus onabotulinumtoxinA, even though antimuscarinics themselves were not comparators of interest. Because such studies were included in a systematic and comprehensive way, they allowed for a more complete evidence network, with additional information regarding antimuscarinic efficacy and safety, and were not anticipated to introduce bias to comparisons of interest. Networks based on direct versus indirect evidence were also compared to assess any potential discrepancies. To be considered for inclusion, eligible studies were required to report on at least one of the efficacy or safety endpoints listed in Supplementary Table 1. Studies including patients with OAB and urinary incontinence with a known cause (eg surgery, pregnancy, benign prostatic hyperplasia, bladder outlet obstruction, spinal

cord injury) or with any of the following conditions: neurogenic OAB, stress urinary incontinence, bladder oversensitivity, or bladder hypersensitivity were excluded. Studies that included mixed populations for which results were not reported separately for idiopathic OAB subgroup, and studies that did not present data in such a way that endpoints for a treatment-experienced population (of at least 80%) could be identified were also excluded. Lastly, cross over studies for which results were not reported before cross over occurred were not included.

Study Identification and Selection. Two reviewers independently reviewed identified abstracts against the study's inclusion and/or exclusion criteria; abstracts included at this stage were subsequently reviewed in full-text. Final assessments by the 2 reviewers were compared for reconciliation. Any discrepancies between the studies selected for inclusion by the 2 researchers were arbitrated by a third reviewer. When the study did not meet either the *a priori* inclusion and/or exclusion criteria, reasons for ineligibility were recorded and a Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart was generated.

Sub-analysis of Initially Excluded Mirabegron Studies. The evidence generated by the systematic search was supplemented by post-hoc analyses conducted on the subset of treatment-experienced patients from mirabegron studies that were initially excluded due to an insufficient proportion of treatment-experienced patients. Results from the post-hoc analyses represent a subset of the overall evidence base; individual patient data were only available from mirabegron studies such that a post-hoc analysis of treatment-experienced patients was not feasible for other comparators. The inclusion of unpublished results where available strengthens the evidence base and is in alignment with the Cochrane Handbook for Systematic Reviews of Interventions.¹⁸

Data Extraction and Quality Assessment. Double data extraction into a customized Microsoft® Excel® data extraction workbook was performed for all efficacy and safety endpoints data of interest from the eligible studies. All other details of interest were extracted by one reviewer and quality checked by a second reviewer. Any discrepancies were resolved through discussion to achieve consensus.

The quality of the available evidence was assessed using the framework of the Grading of Recommendations Assessment, Development and Evaluation Working Group (Supplementary Table 2), where the quality of each included study was graded on a 4 point scale from very low to high.¹⁹

Evidence Synthesis

Following the systematic search and post-hoc analysis, all endpoints for which sufficient evidence was identified for the comparison of mirabegron to onabotulinumtoxinA were compared via a NMA. All networks differentiated between placebo injection, placebo mix, and placebo oral to account for differences in placebo response across the different forms of placebo. Placebo mix refers to "double dummy" designs where both oral and injection placebos were administered to all individuals in the placebo trial arm, oral placebo was administered to individuals receiving an injection intervention, and injection placebo was administered to individuals receiving an oral intervention, in order to maintain blinding.^{12,13} For endpoints for which results did not

vary notably across different placebo responses, a sensitivity analysis was conducted in which the different placebo forms were pooled into a common placebo, simplifying the network and reducing the number of parameters being estimated.

Statistical Analysis. This NMA was conducted using a Bayesian approach, and followed recommendations for the conduct of evidence synthesis set forth by National Institute for Health and Care Excellence Decision Support Unit guidance documents.^{20,21} Continuous endpoints were modeled with a normal likelihood and identity link function. Binary endpoints were modeled with a binomial likelihood and logit link function, and results presented on the odds ratio (OR) scale.

Mirabegron 50 mg was the intervention of interest; to ensure direct comparability of results across NMAs, mirabegron was set as the reference treatment within the analyses (see Fig. 1). Markov chain Monte Carlo simulations (100,000 iterations; 20,000 as burn-in) with Gibbs sampling were run to estimate relative treatment effects. Point estimates were obtained by averaging the estimates across all retained iterations, with the credible interval (CrI) defined by the 2.5th and 97.5th percentiles. For binary endpoints the log-OR scale was used. Vague priors were set for all trial baselines and between-study standard deviation (SD). Both fixed effect (FE) and random effects (RE) models were run, and the RE model was preferred *a priori* given the expectation of residual heterogeneity between studies. The FE model was selected over the RE model only if the deviance information criterion indicated that the former provided better model fit, or the posterior distribution of the SD parameter was not well estimated in the RE model.

Given the Bayesian approach taken (which precludes use of frequentist statistical significance measures), the magnitude of the benefit was described based on the proportion of the CrI that fell on the point estimate side of equivalence: mild if the percentage of the CrI was <90%, moderate if the percentage of the CrI was ≥90%, and strong if the CrI was entirely on one side of equivalence.

Assessment of Inconsistency. Consistent with good practice,²² studies identified in the systematic search were assessed for homogeneity and consistency.

Additional details on the antimuscarinics used to develop the network and on the assessment of inconsistency are available upon request.

RESULTS

Characteristics of Included Studies

In the systematic search, 2858 abstracts were identified, of which 280 were eligible for full-text review. Fifteen articles, representing 13 studies, were eligible for data extraction and synthesis (Fig. 2).^{8,11-17,23-35} The studies by Everaert et al.¹² and Herschorn et al.¹³ reported different endpoints from a single trial;³⁶ the 2 publications were therefore pooled and counted as a single study. Similarly, the results of Dmochowski et al.²⁵ were pooled with those reported in Rovner et al.³³ as the 2 publications described a single trial. The article by Khullar, 2013,²⁶ comparing placebo oral, mirabegron 50 mg and tolterodine 4 mg, was included in the systematic search. However, as this study was

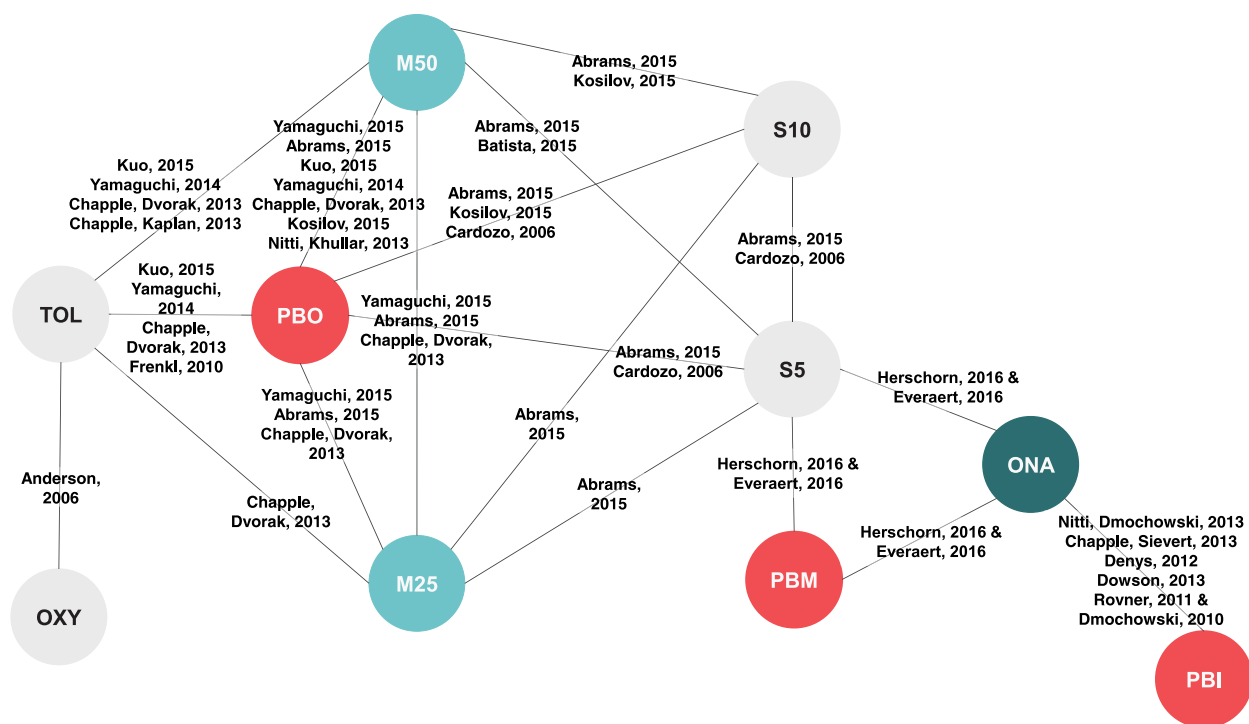


Figure 1. Network meta-analysis network structure

M, mirabegron; ONA, onabotulinumtoxinA; OXY, oxybutynin; PBI, placebo injection; PBO, placebo oral; PBM, placebo mix (injection + oral); S, solifenacin; TOL, tolterodine.

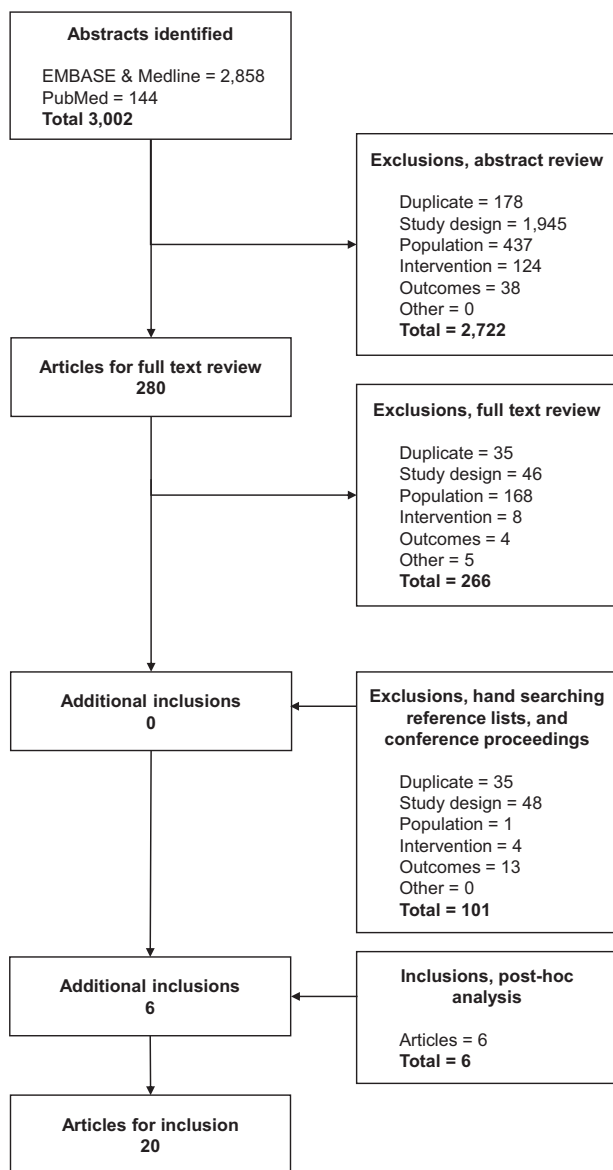


Figure 2. PRISMA flow diagram for study inclusion in the network meta-analysis.

included in the pooled analysis reported by Nitti and Khullar, 2013,²⁷ it was excluded from analysis applicable in the NMA to avoid double counting.

An additional 6 mirabegron studies were included in the post-hoc analysis.^{8,11,15,16,34,35} In the final analysis, 10 studies that assessed mirabegron and 6 that assessed onabotulinumtoxinA were included; none of these directly compared mirabegron with onabotulinumtoxinA. Additionally, two that assessed tolterodine and one that assessed solifenacin were included. The full NMA network structure based on all identified evidence is presented in Figure 1, using mirabegron 50 mg as the reference category.

Patient Characteristics

Baseline patient characteristics were inconsistently reported across the included studies. Among the included studies, the number of patients ranged from 21 to 1887. Across both mirabegron and onabotulinumtoxinA studies, patients were predominantly female; the proportion of female patients ranged from

59.8% to 90.2% in mirabegron study arms and 80.0% to 93.1% in onabotulinumtoxinA study arms. The proportion of patients who were ≥ 65 years of age varied between the 2 treatment groups; across mirabegron study arms, the proportion of patients aged ≥ 65 years ranged from 17.1% to 100.0%, compared to 42.6% to 53.1% among patients in onabotulinumtoxinA study arms. Type of OAB (ie urge urinary incontinence, frequency, and mixed) was not reported across onabotulinumtoxinA trials. Across mirabegron studies, urge urinary incontinence was the most common OAB type reported, making up to 33.3% to 61.0% of patients with OAB.

Network Meta-analysis

Sufficient and consistent evidence was available to analyze the following efficacy and safety endpoints: total micturitions per 24-hours, incontinence episodes per 24-hours, nocturia episodes per 24-hours, patients with UTIs, treatment-emergent adverse events (AEs), treatment-emergent severe AEs, AE-related study discontinuations, overall study discontinuations and voiding difficulty due to dysuria. Due to a lack of sufficient evidence to inform the comparison between mirabegron and onabotulinumtoxinA, daytime micturitions per 24-hours, volume voided per micturition, urinary retention, urgency episodes per 24-hours, and patients with high blood pressure were excluded.

Efficacy

Total Micturitions per 24-Hours. A total of 17 studies^{8,11-17,23-30,32-35} contributed evidence on the number of total micturitions per 24-hours. Estimates of treatment effects for the RE model identified a greater reduction in the total number of micturitions for onabotulinumtoxinA relative to mirabegron 50 mg (0.43 fewer micturitions) although the evidence was not strong in favor of onabotulinumtoxinA (CrI: $-1.22, 0.37$) (Fig. 3). As there was no evidence of different placebo response in this network, placebo forms were subsequently pooled into a common placebo in sensitivity analysis. In this network, onabotulinumtoxinA was strongly associated with greater efficacy for reducing the number of micturitions relative to mirabegron 50 mg, with an estimated 0.64 fewer micturitions (CrI: $-1.01, -0.26$).

Incontinence Episodes per 24-Hours. Eighteen studies^{8,11-17,23-27,29-35} contributed evidence on the number of incontinence episodes per 24-hours. Estimates of treatment effects for the RE model identified that onabotulinumtoxinA was weakly associated with a reduction in the total number of incontinence episodes relative to mirabegron 50 mg (-0.46 fewer incontinence episodes; CrI: $-1.46, 0.53$) (Fig. 3). The efficacy of mirabegron 50 mg relative to placebo varied depending on placebo type. As such, assuming a common placebo for the endpoint of incontinence episodes was not plausible and was not considered in sensitivity analysis.

Nocturia Episodes per 24-Hours. A total of 10 studies^{8,11-13,15-17,29,30,34,35} contributed evidence on the number of nocturia episodes per 24 hours. Estimates of treatment effects for the RE model identified that mirabegron 50 mg was estimated to be similarly efficacious to onabotulinumtoxinA at reducing nocturia episodes (mean difference = 0.03, CrI: $-0.30, 0.38$) (Fig. 3). As there was no evidence of different placebo response under this network, placebos were again pooled into a common placebo in sensitivity analysis. In this analysis, mirabegron 50 mg was

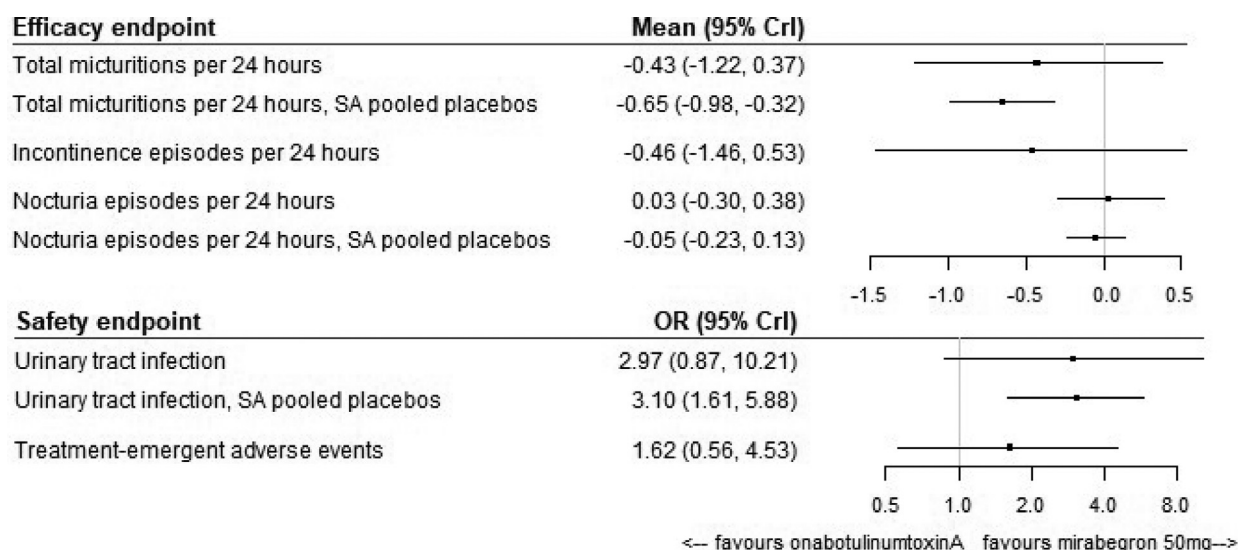


Figure 3. Summary of efficacy and safety results for mirabegron 50 mg compared with onabotulinumtoxinA. CrI, credible interval; OR, odds ratio; SA, sensitivity analysis.

estimated to be similarly efficacious as onabotulinumtoxinA at reducing nocturia episodes.

Safety

Urinary Tract Infections. Estimates of treatment effects on UTIs were informed by 14 studies.^{8,11-13,15-17,23-25,29,30,32-35} In the RE model, onabotulinumtoxinA was associated with greater odds of UTI relative to mirabegron 50 mg (OR = 2.97, CrI: 0.87, 10.21) (Fig. 3), although the strength of the evidence was moderate, as the CrI crossed 1, and it was associated with considerable uncertainty.

No evidence of different placebo response was found for this network, as such, placebos were pooled into a common placebo in sensitivity analysis. For this analysis, there was strong evidence of threefold higher odds of a patient experiencing a UTI when receiving onabotulinumtoxinA relative to mirabegron 50 mg (CrI: 1.61, 5.88).

Treatment-Emergent Adverse Events (AEs). Fourteen studies^{8,11-17,23,25,29,30,32-35} contributed evidence on the number of patients with treatment-emergent AEs. The NMA suggested that the odds of a patient experiencing a treatment-emergent AE were 1.62 times higher for onabotulinumtoxinA relative to mirabegron 50 mg; however, the evidence was not strong (CrI: 0.56, 4.53) (Fig. 3). There was some variation on the relative risk of treatment-emergent AEs depending on the type of placebo, so a network assuming a common placebo was not considered for this endpoint.

Urinary Retention. Cases of urinary retention were reported in the onabotulinumtoxinA studies, with between 6 and 16 cases reported across studies. However, absence of any urinary retention events for mirabegron and antimuscarinics did not allow for establishing relative safety of mirabegron versus onabotulinumtoxinA (ie, indeterminate OR) within the context of the NMA. As such, urinary retention could not be formally assessed.

Additional Safety Endpoints. Overall, large CrIs were obtained for both the FE and RE models conducted for treatment-emergent severe AEs, AE-related study discontinuations, all-cause study discontinuations and voiding difficulty due to dysuria, which yielded uninformative results for these models. Details on these endpoints can be found in Supplementary Materials: Safety Endpoints.

Assessment of Inconsistency. There was no evidence of inconsistency for any endpoint. Results from the assessment of inconsistency are available upon request.

DISCUSSION

The present study characterized the efficacy and safety of mirabegron 50 mg relative to onabotulinumtoxinA 100 U, in patients with OAB previously treated with antimuscarinics, in the absence of direct comparative evidence. In clinical practice, mirabegron and onabotulinumtoxinA are typically reserved for patients who have failed prior treatments with antimuscarinics.⁴ As such, a study that thoroughly compared the efficacy and safety of these therapies is warranted, so that well-informed decisions can be made in clinical practice when selecting subsequent therapy after failure with antimuscarinics.

Results from the NMA demonstrated that onabotulinumtoxinA was strongly associated with a reduction on the number of micturitions in a 24-hour period (0.64 fewer micturitions; CrI: -1.01, -0.26) relative to mirabegron, and weakly associated with reducing the number of incontinence episodes (-0.46; CrI: -1.46, 0.53). There was no evidence of differences in efficacy with either agent for the management of nocturia episodes. With respect to safety, onabotulinumtoxinA was strongly associated with threefold greater odds of UTIs relative to mirabegron (OR = 3.10, CrI: 1.61, 5.88). This analysis did

not provide specific evidence of a different safety profile between the 2 agents for any other safety endpoints investigated in the NMA. Notably, however, while no urinary retention events were reported across the mirabegron studies, this endpoint was reported in 4 of the 6 onabotulinumtoxinA studies, with the number of events across studies ranging from 6 to 16, indicating that this is an important safety consideration for onabotulinumtoxinA.

The findings of this study are similar to those reported in recently published NMAs by Freemantle et al.⁹ and Drake et al.¹⁰ although the efficacy benefits associated with onabotulinumtoxinA were less pronounced, while addressing some key limitations of these studies. Due to the high placebo response reported in OAB trials,^{37,38} an important strength of the current study was that the potential for differences in placebo response was examined and accounted for as applicable, thereby minimizing any bias that may have been introduced into the comparison of interest via effect modification of treatment efficacy by patient characteristics or differences in placebo response. For each endpoint-specific network it was assumed *a priori* that different placebo forms (and associated difference in frequency) were susceptible to different placebo responses, by including different placebo forms as different nodes in the network of evidence. The decision to pool placebos was made only if there was no evidence of different placebo responses (defined by substantial overlap of the CrIs associated to the different placebo forms relative to the reference treatment), and as long as there was enough precision to estimate the relative difference. There was no evidence of different placebo response in the networks of evidence for total micturitions, nocturia episodes, and UTIs. Overall, pooling placebos resulted in narrower CrIs around effect estimates. The evidence suggested a potential for differences in placebo response in the network of urinary incontinence. As such, the network with separate placebos was retained for this endpoint.

Another strength of this study was the focus on a treatment-experienced patient population, which led to a more homogeneous evidence base across studies with respect to disease severity compared to prior NMAs. Freemantle et al.⁹ and Drake et al.¹⁰ included statistical adjustments for imbalances on baseline disease severity via network meta-regression but given substantial differences in treatment history and disease severity between patients enrolled in onabotulinumtoxinA trials relative to mirabegron trials, the data may have been insufficient for appropriately adjusting for those imbalances. Specifically, Freemantle et al.⁹ conducted network meta-regression using aggregate data, as well as individual patient-level data (IPD) from 2 onabotulinumtoxinA studies. The authors acknowledged that the aggregate data were insufficient to accurately estimate the effect of differing baseline disease severity on endpoints and supplemented these with analyses relying on IPD which lacked evidence specific to mirabegron. This limitation of the IPD required assuming the same impact of symptom severity on

endpoints in both mirabegron and onabotulinumtoxinA studies. Although narrowing the focus in the definition of patient population leads to fewer studies informing the analyses, it does not necessarily reduce the precision in generated estimates, as having a heterogeneous mix of patients (ie, treatment-naïve and treatment-experienced patients all with varying levels of symptom severity) can lead to considerable between-study variance. Overall, only mild heterogeneity was present across endpoints (as indicated by small between-study SDs and tight associated CrIs). For some of the safety endpoints, large between-study SDs were likely due to a sparse evidence base, rather than heterogeneity in the evidence base. Although the efficacy results generated by this study are in line with the results reported by Freemantle et al.⁹ and Drake et al.,¹⁰ the magnitude of the estimated effects was lower in the present study. This may be due to having a more homogeneous evidence base. The quality of the available evidence was assessed using the framework of the Grading of Recommendations Assessment, Development and Evaluation Working Group (Supplementary Table 2). All identified studies were determined to be of moderate or high quality.³⁹

Lastly, this study provides a comprehensive overview of the comparability of mirabegron versus onabotulinumtoxinA, with 7 additional studies contributing to the network of evidence. Both efficacy and safety were investigated in this analysis, while the NMAs by Freemantle et al.⁹ and Drake et al.¹⁰ did not report on any safety endpoint, providing only a partial overview on the comparability of the 2 regimens. Overall, onabotulinumtoxinA was strongly associated with a threefold greater risk of UTIs relative to mirabegron. While the analysis did not provide evidence of a different safety profile between the 2 agents for any other safety endpoints investigated in the NMA, it should be noted that the proportion of patients experiencing urinary retention ranged from 5.4% to 10.9% across onabotulinumtoxinA trials and was 0% across mirabegron trials. As such, although urinary retention was reported in enough studies to generate a connected network, as none of the patients treated with mirabegron experienced urinary retention, a formal quantitative assessment of relative safety of mirabegron versus onabotulinumtoxinA could not be performed.

Limitations

There are limitations inherent to NMAs that warrant mention. This NMA incorporated evidence from the subset of eligible treatment-experienced patients in mirabegron studies where the overall population did not meet the inclusion criteria of the systematic search. While these additional data provided important evidence in the comparisons of interest, conducting post-hoc analyses restricts the analysis to only a subset of the overall study population, limiting power and excluding a portion of the mirabegron evidence base. Baseline characteristics were compared between the full study population and the subset of treatment-experienced

patients (data available upon request). Overall, baseline characteristics aligned with those reported in the original studies, suggesting that limiting the population to treatment-experienced patients did not induce other major differences to population makeup. While all NMAs are limited by the heterogeneity of the patient characteristics, the post-hoc analysis was undertaken to create a more homogeneous patient population than previous NMAs conducted in patients with OAB. Potential residual heterogeneity includes the fact that while patients in the mirabegron and antimuscarinics trials may have had prior experience with antimuscarinics, some may not have failed treatment; in contrast, those in onabotulinumtoxinA studies most likely had already failed several other treatments. Given the limited data available, it was not possible to adjust for these potential differences in prior treatment exposure.

CONCLUSION

This study provides a comprehensive overview of the available evidence comparing mirabegron 50 mg with onabotulinumtoxinA 100 U with respect to efficacy and safety. Evidence suggests that although onabotulinumtoxinA is more efficacious at reducing the number of daily micturitions in a treatment-experienced OAB population, relative to mirabegron, it is also associated with an estimated threefold greater risk of UTIs. Furthermore, although the relative safety of urinary retention between onabotulinumtoxinA and mirabegron could not be quantified due to statistical limitation, it was identified as a safety outcome in onabotulinumtoxinA studies. These results suggest that the efficacy benefits associated with onabotulinumtoxinA among treatment-experienced patients may be less pronounced than previously reported among mixed populations with OAB. In the absence of head-to-head comparisons, this study helps to inform the risk-benefit of mirabegron and onabotulinumtoxinA for treatment-experienced patients with OAB, that will assist clinicians and patients with treatment decisions.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.urology.2019.02.005>.

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