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Comparative efficacy and tolerability of solifenacin 5 mg/day versus other oral antimuscarinic agents in overactive bladder: A systematic literature review and network meta-analysis

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Aims: To compare efficacy and tolerability of solifenacin 5 mg/day versus other oral antimuscarinic agents for the treatment of overactive bladder (OAB).

Methods: Literature searches of MEDLINE, Embase, and the Cochrane Library were undertaken to identify randomized controlled trials in OAB (2000-2015) for antimuscarinic agents. A network meta-analysis (NMA) was performed to estimate efficacy and tolerability outcomes for solifenacin 5 mg/day relative to other antimuscarinics.

Results: The NMA included 53 eligible trials (published, $n = 48$; unpublished on search date, $n = 5$). Solifenacin 5 mg/day was significantly more effective than tolterodine 4 mg/day for reducing incontinence and urgency urinary incontinence (UUI) episodes, but significantly less effective than solifenacin 10 mg/day for micturition; no other statistically significant differences were noted for efficacy. Solifenacin 5 mg/day had a statistically significant lower risk of dry mouth compared with darifenacin 15 mg/day, fesoterodine 8 mg/day, oxybutynin extended-release 10 mg/day, oxybutynin immediate-release (IR) 9-15 mg/day, tolterodine IR 4 mg/day, propiverine 20 mg/day, and solifenacin 10 mg/day. There were no significant differences between solifenacin 5 mg/day and other antimuscarinics for risk of blurred vision, or for 11 of 17 active comparators for risk of constipation.

Conclusions: This NMA suggests that the efficacy of solifenacin 5 mg/day is at least similar to other common antimuscarinics across the spectrum of OAB symptoms analyzed, and is more effective than tolterodine 4 mg/day in reducing incontinence and UUI episodes. Solifenacin 5 mg/day has a lower risk of dry mouth compared with several agents.

KEYWORDS
antimuscarinics, blurred vision, constipation, dry mouth, incontinence, micturition, solifenacin

John Heesakkers led the peer-review process as the Associate Editor responsible for the paper.

1 | INTRODUCTION

Overactive bladder (OAB) is a common condition, with an estimated global prevalence of 10.7% (11.6% in women and 9.7% in men) in 2008.[1] OAB is characterized by urinary urgency, and is usually accompanied by frequency and nocturia with or without urgency urinary incontinence (UUI) in the absence of urinary tract infection or other obvious pathology.[2,3] OAB symptoms can cause psychological distress, and have a profound negative impact on health-related quality of life, relationships, and self-esteem.[4]

International clinical practice guidelines recommend patient education, lifestyle advice and bladder training for the initial management of OAB[3,5] or urinary incontinence.[6] Oral antimuscarinic (anticholinergic) agents are recommended if conservative measures fail.[3,5,6] Persistence and adherence with antimuscarinics in clinical practice is, however, poor due to both efficacy and tolerability issues,[7] and evidence suggests there is a limited incremental benefit of subsequent antimuscarinics after the first prescribed agent[8] despite guidance to switch between agents if initial treatment fails.[5,6,9] Understanding which antimuscarinic is best tolerated and most efficacious would enable sensible and ultimately cost-effective first-line decisions.

Randomized controlled trials (RCTs) provide rigorous evidence on the relative effect of different interventions, yet it is impractical to perform comparisons of all antimuscarinics in one clinical trial. In the absence of direct comparisons, indirect comparisons and network meta-analyses (NMAs) are practical alternatives, and provide evidence for selecting the optimum starting treatment(s).[10,11] NMAs use the effects of two treatments versus a common comparator to estimate relative treatment effects.[11]

A systematic literature review and NMA was performed to compare the efficacy and tolerability of oral antimuscarinics versus solifenacin 5 mg/day (Vesicare®) for the treatment of OAB.

2 | MATERIALS AND METHODS

2.1 | Systematic literature review

The literature search followed the Cochrane methodology[12] and was undertaken according to the Centre for Reviews and Dissemination Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[13]

2.1.1 | Search strategy

A literature search of electronic databases, that is, Ovid MEDLINE® In-Process and other non-indexed citations, Ovid MEDLINE®, Embase and the Cochrane Library, was performed to identify RCTs evaluating the efficacy and tolerability of pharmacological treatments approved for OAB. A complementary search of ClinicalTrials.gov was also undertaken for unpublished trials of target treatments. Searches were performed in November 2015 for papers published from 2000 onward. Search strategies are presented in Supplementary appendix S1. In addition, the bibliographies of two previous systematic reviews were checked.[14,15] Three other relevant studies performed by the study sponsor, which were completed but not published at the time of the NMA, were also included (BESIDE [NCT01908829]; SHRINK NCT01093534]; and SYNERGY [NCT01972841]).[16–18] No complementary searches on conference proceedings were undertaken.

2.1.2 | Study selection

Studies were required to meet pre-specified inclusion and exclusion criteria, and written in English or French (Table 1). There was no geographical restriction on where studies were performed or on the severity of OAB across studies.

Publications identified by the searches were assessed independently by two reviewers. The study titles and abstracts were screened for relevance, and full papers were retrieved for studies that appeared to meet the eligibility criteria. Any disagreements between reviewers were resolved by discussion and consensus.

2.1.3 | Data extraction

Double-data extraction was employed. Data were captured in specifically designed extraction forms, which were tested and validated on three randomly selected studies and further refined as needed during the extraction phase. Extracted data included study design, patient characteristics, interventions, outcome results, and study limitations. Multiple publications for one trial were compiled into a single entry.

Efficacy outcomes assessed were micturition episodes, incontinence episodes, and UUI episodes per 24 h; that is, those largely consistent with the International Continence Society (ICS) definition of OAB (excluding urgency and nocturia)[2,3] and often used in clinical studies. Tolerability outcomes assessed were dry mouth, constipation and blurred vision, that is, the most common antimuscarinic side effects.[19] Dedicated software (Grafula® version 1.1, Knowledge Probe Inc; Graphclick®; Arizona Software) was used to extract data from graphs when data were only presented in this way. Authors of eligible studies were not contacted for additional information.

2.1.4 | Quality assessment

Two reviewers independently assessed the included studies for risk of bias and methodological quality using the

TABLE 1 Systematic literature review: inclusion and exclusion criteria

Criterion	Included	Excluded
Population	Men and/or women aged ≥18 years; diagnosis of OAB or detrusor overactivity or urinary urgency	Men and/or women aged <18 years; neurogenic detrusor overactivity; lower urinary tract symptoms associated with benign prostatic hyperplasia
Study design	RCT[a]	Non-RCT; open-label follow-up of RCT; database studies; case reports
Trial length	Any	<8 or >16 weeks for efficacy outcomes and <4 or >16 weeks for tolerability outcomes
Treatments	Studies comparing two or more treatments: solifenacin (5 or 10 mg/day); tolterodine IR or ER (2 or 4 mg/day); fesoterodine (4 or 8 mg/day); imidafenacin (0.2 mg/day); oxybutynin IR or ER (5, 9, 10, or 15 mg/day); propiverine (20 mg/day); trospium chloride (40 or 60 mg/day); darifenacin (7.5, 15, or 30 mg/day); or placebo	Flexible-dose regimens
Outcomes	Efficacy outcomes: micturition;[b] incontinence;[b] urgency;[b] urge urinary incontinence;[b] 50% reduction in incontinence episodes; zero incontinence episodes Tolerability outcomes: dry mouth; constipation; blurred vision	–
Publication type	Full papers	Abstracts, letters, and literature reviews

ER, extended-release; IR, immediate release; OAB, overactive bladder; RCT, randomized controlled trial.
[a]Crossover trials were included if outcomes from the first treatment phase were assessed between 8 and 16 weeks.
[b]Episodes per 24 h.

Cochrane tool,[12] which assesses randomization, blinding, baseline comparability, completeness of reporting, and analysis type. Each study was awarded a grade (yes/no/not clear/not applicable); a high proportion of "no" responses was interpreted as an indication of low quality, and a high proportion of "yes" responses as high quality. Disagreements between reviewers were resolved by discussion and consensus.

2.2 | Network meta-analysis

A Bayesian mixed treatment comparison, a type of NMA,[11] was performed to estimate the relative efficacy and tolerability of solifenacin 5 mg/day versus other oral antimuscarinics in adults with OAB. Antimuscarinics given by intravesical, topical, or transdermal routes were excluded. Inclusion and exclusion criteria for the NMA are shown in Table 2.

2.2.1 | Statistical methods

For efficacy outcomes, means and standard errors of the changes from baseline in numbers of micturition episodes, incontinence episodes, and UUI episodes per 24 h were used as inputs. When the mean change was not reported, it was calculated as the difference between the mean at the end of follow-up and mean at baseline, where available. If the standard error was not reported, it was derived from the standard deviation, variance or confidence interval around the mean, where available. Median changes from baseline were not considered. For adverse events (AEs), the numbers of patients experiencing dry mouth, constipation, or blurred vision and the total number of patients by treatment arm were used as inputs. If the number of patients experiencing the outcome was not reported, the number of patients with the specific outcome was estimated by multiplying the total number of patients in the study arm and the reported percentage of patients experiencing the outcome. For studies reporting zero events in at least one arm, 0.5 was added to the numerator (number of events) and 1 to the denominator (number of patients in each arm).[20] Studies reporting zero events in all arms were not considered for that type of event.[12]

Non-informative prior distributions were applied for the NMA. For each outcome, fixed-effects and random-effects models were estimated. The model with the best quality of fit

TABLE 2 Network meta-analysis: inclusion and exclusion criteria

Criterion	Efficacy	Tolerability
Inclusion criteria		
Study design	Randomized controlled trials	Randomized controlled trials
Patient population	FAS or ITT analyses sets	FAS, ITT, SAF, or PPS analysis sets
Intervention	Studies comparing two or more of the following treatments: darifenacin, solifenacin, tolterodine, fesoterodine, oxybutynin, trospium chloride, propiverine, imidafenacin, or placebo	Studies comparing two or more of the following treatments: darifenacin, solifenacin, tolterodine, fesoterodine, oxybutynin, trospium chloride, propiverine, imidafenacin, or placebo
Duration of follow-up	8-16 weeks	4-16 weeks
Outcomes	Mean change from baseline in the number of micturition/24 h, incontinence/24 h, and UUI/24 h	Number of patients experiencing dry mouth, constipation, and blurred vision
Exclusion criteria	Studies with less than two treatment arms	Studies with less than two treatment arms
	Studies comparing combined treatments	Studies comparing combined treatments
	Flexible-dose studies	Flexible-dose studies
	Studies versus placebo patch	Studies versus placebo patch
	Median change from baseline in the number of micturition/24 h, incontinence/24 h, and UUI/24 h	Criteria for exclusion of results related to one outcome: Zero event in all arms
	Criteria for exclusion of results related to one outcome: Results in the PPS or SAF analysis in sets only, if more than 5% of randomized patients are missing No information on variability available and no possible imputation of the SE based on data for the same treatment from other studies	

FAS, full-analysis set; ITT, intention-to-treat; OAB, overactive bladder; PPS, per-protocol set; SAF, safety analysis set; UUI, urgency urinary incontinence.

was selected (ie, the model with the lowest Bayesian deviance information criterion [DIC]). If the quality of fit was similar between arms (ie, DIC difference <5), the fixed-effects model was selected. The convergence of models was assessed based on three diagnostic tools (Brooks-Gelman-Rubin diagnostic tool in WinBUGS, inspection of the auto-correlation, and history plots).

Analyses were performed using dedicated software, WinBUGS, version 1.4 (MRC Biostatistics Unit, Cambridge, UK). The WinBUGS codes used are shown in Supplementary appendix S2. Summary statistics were presented as the mean change from baseline in number of events versus solifenacin 5 mg/day with 95% credibility intervals (95% CrI) for efficacy outcomes, and odds ratios (OR) with 95% CrI for tolerability outcomes. Forest plots of summary statistics were developed for each outcome. Mean differences (efficacy) or ORs (tolerability) were considered as statistically significant when the associated 95% CrI did not include zero or one, respectively.

A systematic review and meta-analysis reported there were no statistically significant differences for cure/improvement, leakage episodes or micturitions in 24 h for extended-release (ER) versus immediate-release (IR) formulations of oxybutynin or tolterodine.[21] Therefore, in our analysis, ER and IR formulations of oxybutynin and tolterodine were assumed to have similar efficacy and were not separated for efficacy outcomes, but were presented separately for tolerability outcomes.

3 | RESULTS

The PRISMA flow diagram for the literature search is shown in Figure 1. A total of 7,443 references were retrieved after removal of duplicates, of which 6,815 were excluded after a review of the title and/or abstract. The 628 remaining articles were obtained as full-text articles of which 575 were excluded for not meeting the eligibility criteria. A total of 53 studies were included in the NMA, including five studies which had not been published on MEDLINE at the time of analysis. No studies were considered to be at high risk of bias and all were included in the NMA (Supplementary appendix S3).

Comparators in the trials were placebo (40 trials), tolterodine ER (16 trials), tolterodine IR (11 trials), solifenacin 10 mg/day (10 trials), fesoterodine (9 trials), oxybutynin IR (5 trials), oxybutynin ER (4 trials), trospium chloride (5 trials), darifenacin (4 trials), propiverine (2 trials), and imidafenacin (1 trial). A summary of the studies in the

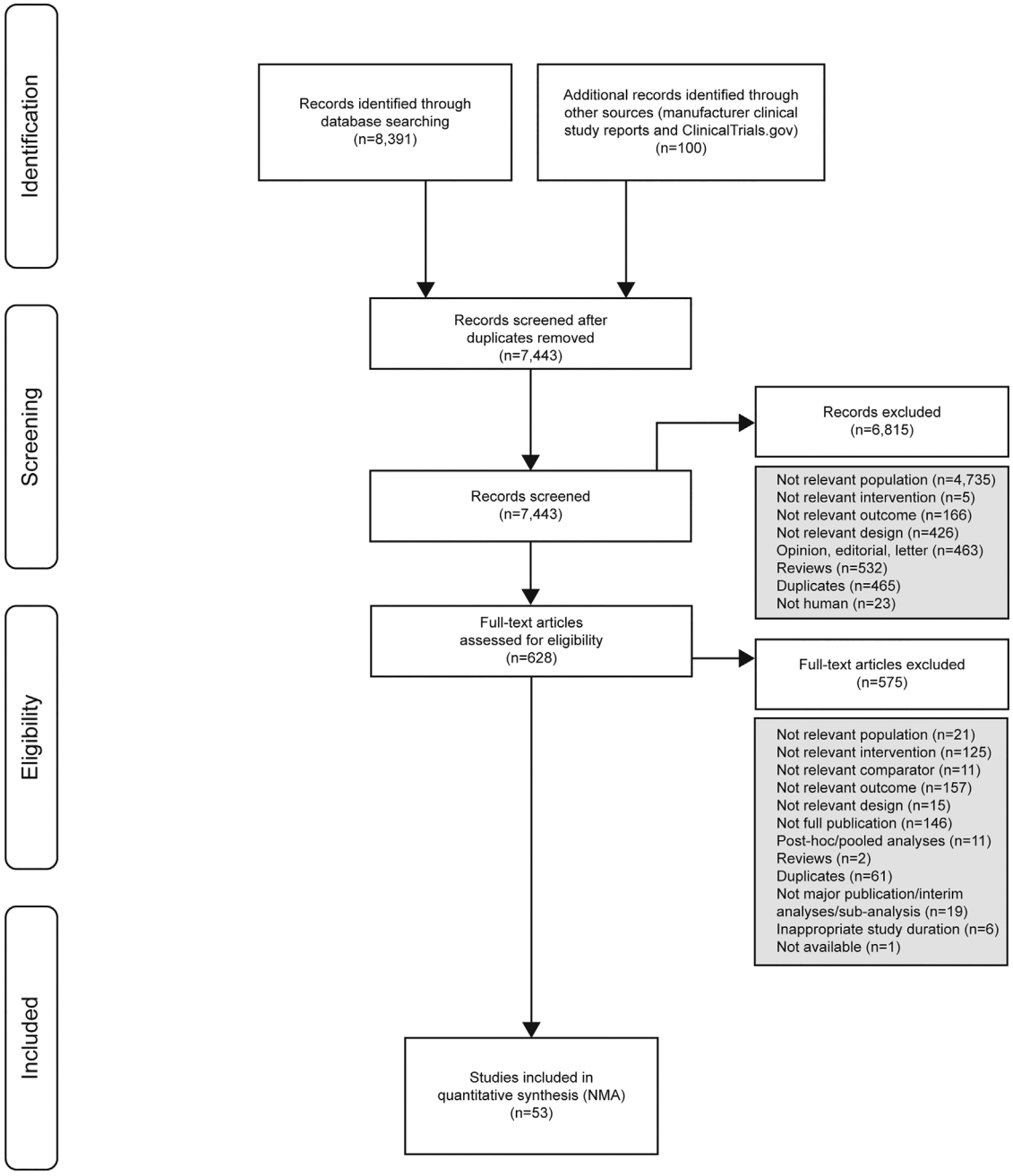

FIGURE 1 PRISMA flow diagram.
NMA, network meta-analysis

NMA is presented in Supplementary appendix S4, and the studies used for the efficacy and tolerability outcomes are presented in Supplementary appendix S5.

3.1 | Efficacy outcomes

Forest plots for the efficacy outcomes are shown in Figure 2. Network diagrams, which show all direct comparisons included in the analysis, and tabulated results are shown in Supplementary appendices S6 and S7, respectively. Random-effect models were used for micturition frequency and UUI, and fixed-effect model for incontinence based on the DIC.

3.1.1 | Micturition frequency

The NMA of micturition was based on 32 trials ($n = 25\,612$) (Supplementary appendix S5). No statistically significant differences were observed with solifenacin 5 mg/day compared with the other antimuscarinics. Solifenacin 10 mg/day was significantly more effective than solifenacin 5 mg/day in reducing micturition frequency (mean difference, −0.261 [95% CrI: −0.501, −0.028]) (Figure 2A).

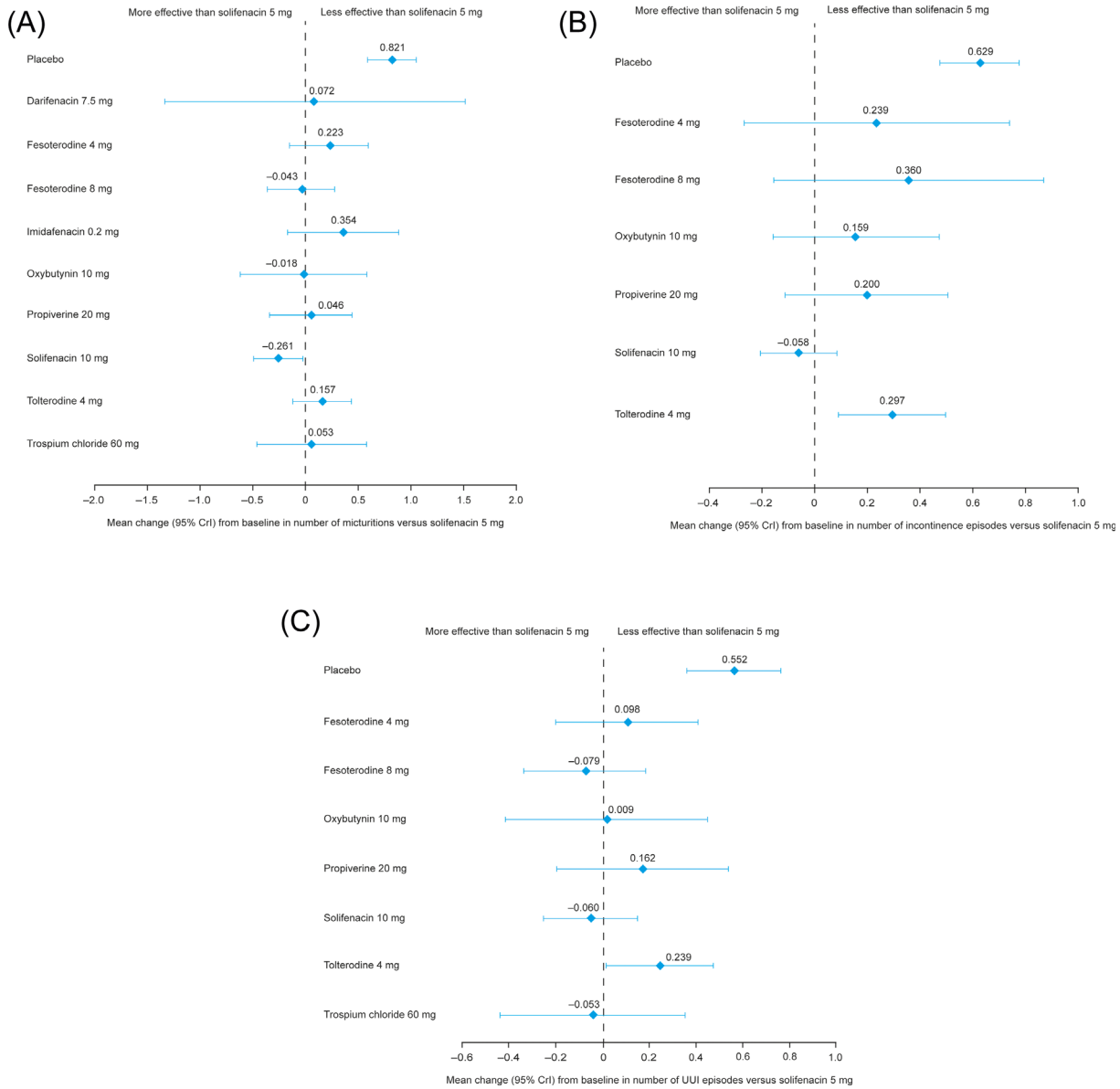

FIGURE 2 Efficacy outcomes versus solifenacin 5 mg/day:* A, Mean change from baseline in the number of micturition episodes/24 h; B, Mean change from baseline in the number of incontinence episodes/24 h; C, Mean change from baseline in the number of urge urinary incontinence episodes/24 h. Error bars indicate the 95% CrI for each mean estimate. If the 95% CrI around the difference includes zero, a treatment has similar efficacy versus solifenacin 5 mg/day. If the upper limit of the 95% CrI around the difference is less than zero, a treatment is significantly more efficacious than solifenacin 5 mg/day. If the lower limit of the 95% CrI around the difference is higher than zero, a treatment is significantly less efficacious than solifenacin 5 mg/day. *A summary of studies included in the NMA are listed in Supplementary appendix S4; studies included in the analysis for each endpoint are listed in Supplementary appendix S5; and network diagrams to show all direct comparisons made in the analysis (per endpoint) are included in Supplementary appendix S6. CrI, credible interval; NMA, network meta-analysis; UUI, urgency urinary incontinence

3.1.2 | Incontinence

The NMA of incontinence was based on 18 trials ($n = 10\,440$) (Supplementary appendix S5). Solifenacin 5 mg/day was statistically significant versus tolterodine 4 mg/day (mean difference, 0.297 [95% CrI: 0.093, 0.499]) in reducing incontinence episodes. There was a trend towards better efficacy with solifenacin 5 mg/day compared with the other comparators (except solifenacin 10 mg/day), but none of the differences were statistically significant (Figure 2B).

3.1.3 | Urgency urinary incontinence

The NMA of UUI was based on 29 trials ($n = 20\,215$) (Supplementary appendix S5). Solifenacin 5 mg/day was statistically significant versus tolterodine 4 mg/day (mean difference, 0.239 [95% CrI: 0.012, 0.467]) in reducing

episodes of UUI. No significant differences were observed for solifenacin 5 mg/day versus any of the other comparators (Figure 2C).

3.2 | Tolerability outcomes

Forest plots for the tolerability outcomes are shown in Figure 3. Network diagrams and tabulated results are shown in Supplementary appendices S6 and S7, respectively. A fixed-effect model was the best-fitting model for all tolerability outcomes.

3.2.1 | Dry mouth

Fifty-two trials ($n = 32\,510$) reported the incidence of dry mouth (Supplementary appendix S5). A statistically significant higher risk of dry mouth compared with solifenacin 5 mg/day was observed for nine of 19 active comparators: darifenacin 15 mg/day (OR, 2.018 [95% CrI: 1.472, 2.997]), fesoterodine 8 mg/day (OR, 2.440 [95% CrI: 1.973, 3.050]), oxybutynin ER 10 mg/day (OR, 1.594 [95% CrI: 1.171, 2.243]) or oxybutynin IR 9 mg/day (OR, 2.679 [95% CrI: 1.802, 3.918]), 10 mg/day (OR, 3.539 [95% CrI: 2.151, 6.228]), or 15 mg/day (OR, 9.280 [95% CrI: 5.303, 18.478]), propiverine 20 mg/day (OR, 1.573 [95% CrI: 1.343, 2.226]), solifenacin 10 mg/day (OR, 2.274 [95% CrI: 1.919, 2.676]), and tolterodine IR 4 mg/day (OR, 1.720 [95% CrI: 1.326, 2.073]) (Figure 3A). No significant differences were observed between solifenacin 5 mg/day and the remaining 10 active comparators.

3.2.2 | Constipation

Forty-six trials ($n = 31\,564$) reported the incidence of constipation (Supplementary appendix S5). In 11 of 17 active treatment comparisons, there were no statistically significant differences observed between solifenacin 5 mg/day and other antimuscarinics (Figure 3B). The exceptions were solifenacin 10 mg/day, which was associated with a significantly higher risk of constipation (OR, 1.792 [95% CrI: 1.420, 2.276]), while tolterodine IR 4 mg/day (OR, 0.491 [95% CrI: 0.321, 0.737]) or ER 4 mg/day (OR, 0.585 [95% CrI: 0.402, 0.845]), fesoterodine 4 mg/day (OR, 0.501 [95% CrI: 0.312, 0.800]) and oxybutynin ER 10 mg/day (OR, 0.498 [95% CrI: 0.278, 0.883]) were associated with a significantly lower risk of constipation compared with solifenacin 5 mg/day.

3.2.3 | Blurred vision

Twenty-one trials ($n = 17\,366$) reported the incidence of blurred vision (Supplementary appendix S5). There were no statistically significant differences between solifenacin 5 mg/day and any of the other antimuscarinics, except for solifenacin 10 mg/day which was associated with a significantly higher risk of blurred vision (OR, 1.513 [95% CrI: 1.068, 2.158]) (Figure 3C).

4 | DISCUSSION

This NMA, based on data from 53 RCTs, suggests that solifenacin 5 mg/day is more effective than tolterodine 4 mg/day in the relief of incontinence and UUI episodes in adults with OAB, but does not differ significantly compared with other antimuscarinics (except solifenacin 10 mg/day) for the other efficacy outcomes assessed. The NMA also showed that solifenacin 5 mg/day had a lower risk of dry mouth than darifenacin 15 mg/day, fesoterodine 8 mg/day, tolterodine IR 4 mg/day, oxybutynin (IR 9-15 mg/day or ER 10 mg/day), propiverine 20 mg/day, and solifenacin 10 mg/day. The risk of blurred vision did not differ significantly across all antimuscarinics, and the risk of constipation also did not differ significantly between solifenacin 5 mg/day and 11 of 17 comparator antimuscarinics.

The NMA allowed different doses of antimuscarinics to be assessed. The higher solifenacin dose (10 mg/day) appeared to significantly reduce micturition frequency compared with solifenacin 5 mg/day, but was associated with a significantly higher risk of AEs (ie, dry mouth, blurred vision, constipation). No significant differences in the efficacy outcomes were observed in comparisons of solifenacin 5 mg/day with the low and high doses of fesoterodine. Similar to solifenacin 10 mg/day, the significant differences in dry mouth versus solifenacin 5 mg/day were observed with the higher dose options of darifenacin, fesoterodine, tolterodine IR, oxybutynin IR, and oxybutynin ER. The implication of these findings is that increasing the dose of a specific antimuscarinic should be considered with the potential for reduced tolerability.

Persistence with OAB medication in clinical practice is poor[22–24] and challenging for the management of OAB. Treatment discontinuation can be related to many factors, including inadequate drug efficacy, intolerable AEs, dosing frequency, patient expectations, and cost.[24] However, AEs associated with antimuscarinics are recognized as a common cause of non-adherence;[24] dry mouth, the most prevalent AE,[6] often leads to discontinuation of therapy.[25] Further, incremental improvements in incontinence outcomes achieved by switching between antimuscarinics may be minimal.[8] Selecting the drug that offers the best balance of efficacy and tolerability is an important step in the treatment of patients with OAB,[26] and findings from this NMA suggest that solifenacin 5 mg/day may be the optimum treatment relative to other antimuscarinics for providing this balance.

These data add to the knowledge base and may help guide clinical practice. Some treatment guidelines provide

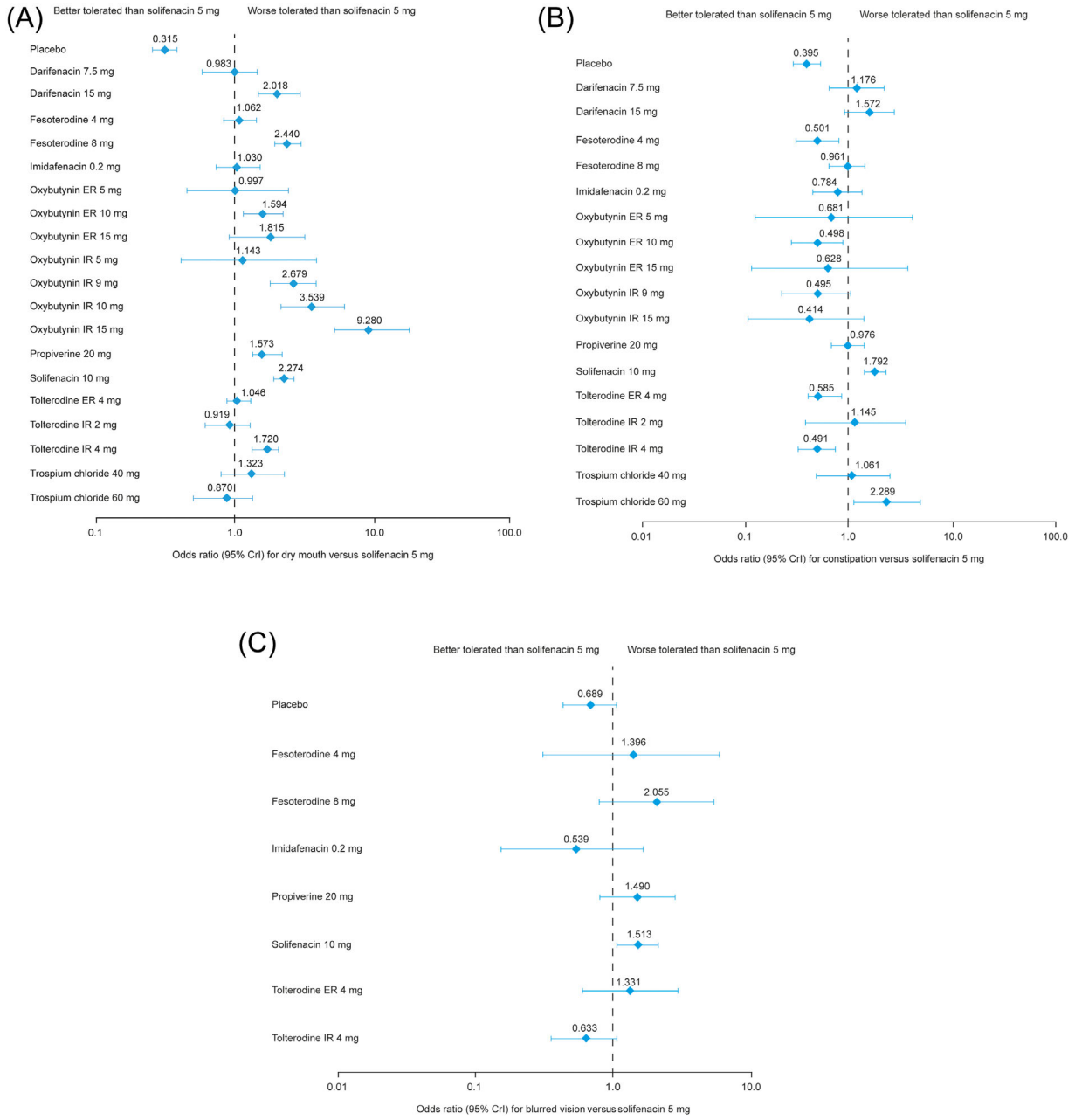

FIGURE 3 Tolerability outcomes versus solifenacin 5 mg/day:

* A, Odds ratios for occurrences of dry mouth; B, Odds ratios for occurrences of constipation; C, Odds ratios for occurrences of blurred vision. Error bars indicate the 95% CrI for odds ratios. If the 95% CrI around the difference includes 1, a treatment has similar safety versus solifenacin 5 mg/day. If the upper limit of the 95% CrI around the difference is less than 1, a treatment is significantly better tolerated than solifenacin 5 mg/day. If the lower limit of the 95% CrI around the difference is higher than 1, a treatment is significantly less well tolerated than solifenacin 5 mg/day.

*A summary of studies included in the NMA are listed in Supplementary appendix S4; studies included in the analysis for each endpoint are listed in Supplementary appendix S5; network diagrams showing all direct comparisons in the analysis (per endpoint) are included in Supplementary appendix S6; and an estimate of treatment effect versus solifenacin 5 mg/day for each outcome are included in Supplementary appendix S7. CrI, credible interval; ER, extended-release; IR, immediate-release

no specific guidance for selecting one antimuscarinic over another,[3,6] whereas UK guidelines for urinary incontinence in women suggest to offer oxybutynin IR, tolterodine IR, or darifenacin as initial treatment followed by a drug with a low acquisition cost if the first treatment is ineffective or poorly tolerated.[9] Formulating guidance on acquisition costs alone does not account for relative efficacy or tolerability, nor does it consider other treatment-related

costs (eg, healthcare provider visits and drug failure/switching) on the overall cost-effectiveness of treatment. The National Institute for Health and Care Excellence (NICE) guidelines were also formulated before the option of treating with a β_3-adrenoceptor agonist as first-line pharmacotherapy or after failure of an antimuscarinic, as recommended in more recent treatment guidelines.[5,6] Selecting the optimum pharmacotherapy, so that it can be integrated with other pharmacological options, is a key step in the cost-effective management of patients with OAB.

The findings of superior effectiveness with solifenacin 5 mg/day compared with tolterodine 4 mg/day for reducing incontinence and UUI frequency concur with two other meta-analyses.[21,27] Madhuvrata et al[21] reported significantly fewer leakage episodes/24 h and urgency episodes/24 h with solifenacin 5 mg/day versus tolterodine ER or IR 4 mg/day. The other meta-analysis, showed significant benefits for solifenacin compared with tolterodine ER or IR 4 mg/day in micturitions/24 h, urgency episodes/24 h, and incontinence episodes/24 h, although all solifenacin doses were combined in this analysis.[27] Also, as in our analysis, both meta-analyses showed that solifenacin 10 mg/day was more effective than solifenacin 5 mg/day in reducing micturitions/24 h but was associated with a significantly higher risk of dry mouth,[21,27] although the rates of constipation and blurred vision were similar with both doses in one meta-analysis.[27]

Most previous meta-analyses comparing antimuscarinics in the treatment of OAB have used traditional methods, that is, included only studies which compare the same interventions.[14,21,27–29] As most RCTs generally include one or two active comparators and placebo, these analyses are limited in their ability to compare different antimuscarinics. NMAs are an extension of traditional meta-analyses and use both direct comparisons (where available) and indirect comparisons to estimate the relative effect of two treatments. Buser et al[30] performed an NMA of efficacy and tolerability of antimuscarinics in OAB relative to placebo. While it is not possible to directly compare their findings with our own because of the different reference treatment, it is of interest that solifenacin 5 mg/day was the second ranked treatment (out of 21 treatments and dosages applied in clinical practice) when evaluated using a single weighted global score for all AEs.[30]

Because randomization does not hold across clinical trials, NMAs may be affected by confounding bias caused by differences between trials. To reduce heterogeneity between study populations in the present analysis, the search was limited to papers published from 2000 onward which were more likely to have adopted the ICS definition of OAB.[2,3] Despite this restriction, we acknowledge that there are other potential sources of heterogeneity among the trials selected. These included differences in study populations (eg, mixed types of incontinence, single and mixed genders, and geographic regions), follow-up assessment times for efficacy and tolerability outcomes (range, 4-16 weeks), and study size (range, 18-3527 subjects). For each of the outcomes, both fixed- and random-effects models were applied and the model with the best fit was selected. Random-effects models that explicitly model heterogeneous data were used for all two efficacy outcomes. However, adjustment of study-level covariates using a meta-regression model, which is a recognized method for reducing the impact of confounding bias,[11] was not performed for our analysis because the covariate level was not available for all studies.

Strengths of this analysis were the large number of studies included, and that each RCT was critically assessed for bias using a recognized tool to eliminate threats to internal validity. While these outcomes were common to many trials and allowed our estimates to include large patient numbers, the analysis is not comprehensive with respect to all possible OAB symptoms (ie, nocturia) and treatment-related AEs. Other limitations include reduced level of access to unpublished studies for the antimuscarinics apart from solifenacin, and excluding conference proceedings from the literature search strategy.

It should also be noted that this study excluded mirabegron, the β_3-adrenoceptor agonist, as an active comparator treatment. Similar overall efficacy and significantly improved tolerability for dry mouth were observed for mirabegron 50 mg/day versus antimuscarinics in a systematic literature review and NMA, which included data from 44 RCTs ($n = 27\,309$).[31] Maman et al reported no significant differences in micturition frequency, incontinence episodes and UUI episodes, but a significantly higher risk of dry mouth and constipation with solifenacin 5 mg/day versus mirabegron 50 mg/day.

5 | CONCLUSIONS

Identifying the optimum antimuscarinic agent is a key step in the effective management of patients with OAB. This NMA suggests that solifenacin 5 mg/day is more effective than tolterodine 4 mg/day in reducing OAB incontinence and UUI episodes, but does not differ significantly in terms of efficacy compared with other oral antimuscarinics. Solifenacin 5 mg/day has a lower risk of dry mouth compared with approximately half of the antimuscarinic agents assessed. Relative to a selection of other oral antimuscarinics, solifenacin 5 mg/day appears to offer a good balance of efficacy and tolerability, endorsing it as a key pharmacotherapeutic option for the treatment of adults with OAB.

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CONFLICTS OF INTEREST

J Nazir, Z Hakimi, and C Mankowski are full-time employees of Astellas Pharma, Inc; C Kelleher has received travel and relevant expenses for meeting attendance and symposium presentations from Astellas Pharma, Inc; S Aballéa and K Maman are employed by Creativ-Ceutical, which has received research grants from Astellas Pharma, Inc; I Odeyemi was employed by Astellas Pharma, Inc at the time of study analysis.

AUTHORS' CONTRIBUTIONS

Study design/protocol development: CK, IO, JN, KM, SA, ZH, CM. Data collection or management: KM, SA. Data analysis and interpretation: CK, IO, JN, KM, SA, ZH, CM. Manuscript writing/editing: CK, IO, JN, KM, SA, ZH, CM. Final version approval of publication: CK, IO, JN, KM, SA, ZH, CM.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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