Methods Research Report

Case Study Comparing Bayesian and Frequentist Approaches for Multiple Treatment Comparisons

Agency for Healthcare Research and Quality
Advancing Excellence in Health Care • **www.ahrq.gov**

Methods Research Report

Case Study Comparing Bayesian and Frequentist Approaches for Multiple Treatment Comparisons

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Contract No. 290-2007-10064-I2

Prepared by:
Minnesota Evidence-based Practice Center
Minneapolis, MN

Investigators:
Bradley P. Carlin, Ph.D.
Hwanhee Hong, Ph.D. candidate
Tatyana A. Shamliyan, M.D., M.S.
François Sainfort, Ph.D.
Robert L. Kane, M.D.

AHRQ Publication No. 12(13)-EHC103-EF
March 2013

This report is based on research conducted by the Minnesota Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2007-10064-I2). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

This report may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.

Persons using assistive technology may not be able to fully access information in this report. For assistance contact shaml005@umn.edu.

None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.

Suggested citation: Carlin BP, Hong H, Shamliyan TA, Sainfort F, Kane RL. Case Study Comparing Bayesian and Frequentist Approaches for Multiple Treatment Comparisons. (Prepared by the Minnesota Evidence-based Practice Center under Contract No. 290-2007-10064-I2.) AHRQ Publication No. 12(13)-EHC103-EF. Rockville, MD: Agency for Healthcare Research and Quality. March 2013. www.effectivehealthcare.gov/reports/final.cfm.

Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies and strategies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To improve the scientific rigor of these evidence reports, AHRQ supports empiric research by the EPCs to help understand or improve complex methodologic issues in systematic reviews. These methods research projects are intended to contribute to the research base in and be used to improve the science of systematic reviews. They are not intended to be guidance to the EPC program, although may be considered by EPCs along with other scientific research when determining EPC program methods guidance.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality. The reports undergo peer review prior to their release as a final report.

We welcome comments on this Methods Research Project. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

Carolyn M. Clancy, M.D.
Director
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.
Director, Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.
Director
Evidence-based Practice Program
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Parivash Nourjah, Ph.D.
Task Order Officer
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Case Study Comparing Bayesian and Frequentist Approaches for Multiple Treatment Comparisons

Structured Abstract

Objectives. Bayesian statistical methods are increasingly popular as a tool for meta-analysis of clinical trial data involving both direct and indirect treatment comparisons. However, appropriate selection of prior distributions for unknown model parameters and checking of consistency assumptions required for feasible modeling remain particularly challenging. We compared Bayesian and traditional frequentist statistical methods for multiple treatment comparisons in the context of pharmacological treatments for female urinary incontinence (UI).

Data Sources. We searched major electronic bibliographic databases, U.S. Food and Drug Administration reviews, trial registries, and research grant databases up to November 2011 to find randomized studies published in English that examined drugs for urgency UI on continence, improvements in UI, and treatment discontinuation due to harms.

Review Methods. We fitted fixed and random effects models in frequentist and Bayesian frameworks. In a hierarchical model of eight treatments, we separately analyzed one safety and two efficacy outcomes. We produced Bayesian and frequentist treatment ranks and odds ratios (and associated measures of uncertainty) across all bivariate treatment comparisons. We also calculated the number needed to treat (NNT) to achieve continence or avoid harms from pooled absolute risk differences.

Results. While frequentist and Bayesian analyses produced broadly comparable odds ratios of safety and efficacy, the Bayesian method's ability to deliver the probability that any treatment is best, or among the top two such treatments, offered a more meaningful clinical interpretation. In our study, two drugs emerged as attractive because while neither had any significant chance of being among the least safe drugs, both had greater than 50 percent chances of being among the top three drugs in terms of Best12 probability for one of the efficacy endpoints.

Conclusions. Bayesian methods are more flexible and their results more clinically interpretable but require more careful development and specialized software.

Key Messages

- Both Bayesian and frequentist hierarchical models can be effective in multiple treatment comparisons.
- Bayesian models sensibly shrink estimates towards each other, encouraging more borrowing of statistical strength from the entire collection of studies. Bayesian methods also lead to more clinically interpretable results (through their ability to assign probabilities to events), as well as more sensible rankings of the pharmacological treatments as compared to traditional NNT-based methods.
- Further development of hierarchical Bayesian multiple treatment comparison methods is warranted, especially for nonbinary data models, simultaneous decisionmaking across multiple endpoints, assessing consistency, and incorporating data sources of varying quality (e.g., clinical vs. observational data).

Contents

Introduction

There is growing interest in assessing the relative effects of treatments by comparing one with another.[1-3] Because few studies are typically available to provide evidence from direct head-to-head comparisons; we must frequently rely on *indirect* comparisons that use statistical techniques to estimate the treatment effects from studies of each given treatment against controls under an assumption of consistency.[4-8] The problems with such systematic reviews, meta-analysis, and synthesis in general are that the circumstances of each study and the samples examined may vary and controls may differ among studies.

A number of techniques have been proposed to address this challenge.[6-8] *Mixed (or multiple) treatment comparisons* (MTCs), sometimes called *network meta-analysis,* refers to methods that compare treatments by combining all available evidence from studies that form a network of evidence (including studies comparing three or more treatment arms) in the absence of direct head-to-head comparisons. By synthesizing direct and indirect comparisons, we can improve the precision of estimates for treatment effects. While frequentist methods for MTCs certainly exist, they become increasingly difficult to fit less constrained models. A Bayesian analysis can easily construct such complicated models with less assumptions and permits explicit posterior inference regarding the probability that each treatment is "best" for a specific outcome.[9-11]

Two major issues to be considered in MTC meta-analysis are *statistical heterogeneity* and *evidence inconsistency*.[11-13] Statistical heterogeneity represents effect size variability between studies. Since each study is conducted under different conditions and populations, study-specific effect sizes may vary even when they are drawn from an underlying population of study effects that has a common mean. Evidence inconsistency is another source of incompatibility that arises between direct and indirect comparisons. In many MTCs, it is possible to make both direct and indirect comparisons for some pairs of treatments. When discrepancies exist between direct and indirect comparisons in terms of size and directionality, these deviations are called evidence inconsistency.

We conducted a systematic literature review that analyzed clinical comparative efficacy of pharmacological treatments for urgency urinary incontinence (UI) in adult women.[14] Urgency UI is defined as involuntary loss of urine associated with the sensation of a sudden, compelling urge to void that is difficult to defer.[15] Continence (complete voluntary control of the bladder) has been considered a primary goal in UI treatment[16,17] and is the most important outcome associated with quality of life in women with UI.[18] We synthesized rates of continence, improvements in UI, and discontinuation of the treatments due to adverse events (AE) of drugs from 83 randomized controlled trials (RCTs).[14] This review utilized traditional frequentist meta-analysis techniques and concluded that drugs for urgency UI have comparable efficacy, and that the magnitude of the benefits from such drugs is small. As such, treatment decisions should be made based on comparative safety of the drugs. Few head-to-head trials were available to provide direct estimates of the comparative efficacy of the drugs.

In this report we introduce general hierarchical models to fit such data and applied both Bayesian and frequentist approaches to estimate the comparative efficacy and safety of selected drugs.[19,20] Also, we introduce more complex Bayesian hierarchical models that account for evidence inconsistency. We compare the frequentist and Bayesian approaches and provide tools to find the best treatment by using some metrics and clinically useful summary statistics that have meaning for patients and practitioners.

Data

We reviewed studies from 1966 to November 2011. Search strategies are described elsewhere.[14] We included RCTs that combined men and women if they reported outcomes in women separately or included more than 75 percent women. We excluded studies of children, adolescents, or men, studies of incontinence caused by neurological disease, and studies of dual fecal and urinary incontinence. We considered urgency UI cases. Most studies did not report the inclusion of mixed UI but some trials included patients with mixed UI as well as urgency UI. We did not find consistent statistically significant effect modification via investigation of whether inclusion of mixed UI modified the effects of the drugs on the outcomes. All trials enrolled patients with overactive bladder (OAB), and all examined drugs were approved by the U.S. Food and Drug Administration (FDA) for OAB. We pooled the trials that reported UI at baseline and also those trials that reported UI-related outcomes (such as OAB) along with UI, and did not find evidence of incomparability across these two groups.

Following FDA and other professional guidelines,[17,21] we focused on patient-centered outcomes and considered only three outcomes: continence, improvement in UI, and discontinuation due to AE, as defined in Table 1. In contrast with previously published Cochrane reviews that combined continence or improvement in UI as one outcome, we analyzed better defined continence separately from improvement in UI. We used discontinuation due to AE as our safety endpoint because this addressed women's perception of the burden and seriousness of the adverse effects, as well as adherence to the treatments. When a woman stops taking a drug due to intolerable adverse effects, no further clinical decisions can be made regarding the drug that caused these effects.

Regarding dosage selection, not all studies had the same dose levels, leading to possible heterogeneity, but for a specific drug, a majority of the studies had the same dose level, while a few studies investigated different dose levels. However, we did not consider separate dose levels as separate treatments since our data were too sparse. Most studies investigated only one dose; there were just one or two studies considering multi-dose levels; in these cases, we selected the higher, more prevalent dose level.

Among 83 RCTs, 65 studies are included for our analysis. Table 2 displays the data, where the information in each cell takes the form 'continence, UI improvement, discontinuation of the study; sample size', with an "N" indicating no response in that category. Figure 1 exhibits the network between drugs for each outcome. The size of each node represents the number of studies investigating the drug, and the thickness of each edge corresponds to the total number of samples for the relation. There are 19 studies for continence, 28 studies for the UI improvement outcome, and 47 studies for discontinuation. Panel (a) shows that none of the studies for the continence outcome included darifenacin as a treatment arm. Panel (c) displays much more complex network structure for the discontinuation outcome, including several drug-to-drug comparisons.

Methods

Bayesian Approach

For Bayesian analyses, hierarchical statistical meta-analysis for multiple treatment comparisons with binary outcomes, which has a long history in the literature,[22-26] was used to address the research questions. We began by fitting four logit models initially proposed by Lu and Ades,[25] who suggest a fully Bayesian hierarchical approach[27] to estimate a relative effect of two treatments, using a log odds ratio of the magnitude of the two effects in the binary case.

We assume that the data from each study follows a binomial distribution. That is,

$$r_{ik} \sim \text{Bin}(n_{ik}, p_{ik}),\ i = 1, 2, \ldots, I,\ k = 1, 2, \ldots, K,$$

where r_{ik} is the total number of events, n_{ik} is the total number of subjects, and p_{ik} is the probability of the outcome in the k^{th} treatment arm from the i^{th} study, with k = 1 for the placebo arm. Logistic regression is commonly used to fit this type of data. The model can be written as

$$\text{logit}(p_{ik}) = \mu_{iB} + \Delta_{Bk},$$

where B represents a baseline treatment (the treatment assigned the smallest k value in each study, and usually placebo), μ_{iB} is the effect of the baseline treatment in the i^{th} study, and Δ_{Bk} is the log odds ratio between the k^{th} treatment and the baseline treatment. For inference, we define d_k as the log odds ratio between treatment k and placebo, with $d_1 = 0$, and the model above can be replaced to

$$\text{logit}(p_{ik}) = \mu_{iB} + d_k - d_B,$$

where Δ_{Bk} is obtained from $d_k - d_B$. Since d_k is the parameter compared to placebo, this can be used for our inferences regarding estimation and ranking of the treatment effects.

Models

Our first three models are fitted under the assumption of evidence consistency; namely, that the estimated effect sizes arising from direct and indirect comparisons are the same. For example, when we compare treatments 2 and 3, we assume we can define $\Delta_{23} = \Delta_{3C} - \Delta_{2C}$, where C indicates the common comparator treatment. We first fit a purely fixed effects model that further assumes all studies estimate the same effect size, and therefore there is no variability (heterogeneity) between studies. In this model, we assume the log odds ratios, $\Delta_{Bk,}$ are the same in each study.

To allow heterogeneity between studies, random effects models may be considered. In this approach, Δ_{Bk} is replaced with δ_{iBk}, which represents a log odds ratio between treatment k and B in the i^{th} study, and we assume an independent normal specification for the δ_{iBk}, i.e.,

$$\delta_{iBk} \sim N(d_k - d_B, \sigma^2).$$

By assigning a distribution to δ_{iBk}, the model can capture the variability among studies. In this random effects model, we assume homogeneous variance σ^2 across all k treatments; we call this homogeneous random effects model. Alternatively, we can introduce heterogeneous variances σ_{Bk}^2 rather than σ^2 in the above distribution across treatments, called heterogeneous random effects model. For a multi-arm trial, there are more than two log odds ratios, and one can account for correlations among them. In this case, we assume $\boldsymbol{\delta_i}$ vector follows a multivariate normal distribution with common correlation of 0.5 among treatment, and we used a conditional normal distribution for each element of $\boldsymbol{\delta_i}$ (see Appendix A).[25]

Our last Bayesian model allows for evidence inconsistency by adding a set of terms called *w-factors* into the model. This approach captures the discrepancy between direct and indirect comparisons between two treatments (say, 2 and 3) as

$$\Delta_{23} = \Delta_{3C} - \Delta_{2C} + w_{C32},$$

where w_{C32} is the w-factor between drugs 2 and 3 through the common comparator treatment C. One can only define the w-factor when the three relative effects (Δ_{23}, Δ_{3C}, and Δ_{2C} in the above equation) are estimable from independent studies. Here, we assume homogeneous variance for random effects and denote this model as inconsistency random effects model. Our data permit addition of two inconsistency factors for the UI improvement outcome (w_{137} and w_{147}) and six w-factors for the discontinuation outcome (w_{124}, w_{137}, w_{147}, w_{148}, w_{156}, and w_{167}). Note that we number the drugs alphabetically except for placebo; i.e., placebo is drug number 1, darifenacin is 2, fesoterodine is 3, and so on. For the continence outcome, we cannot fit this model because no inconsistency w-factors are identified by these data; there are not enough studies having independent sources of direct and indirect comparisons to make these factors estimable.

Prior Distributions

Noninformative Prior

In Bayesian analysis, prior information can be explicitly incorporated. We investigate two sets of prior distribution: one fully noninformative (or "flat") prior and another that encourages shrinkage of the random effects toward their grand means. In the first approach, which we term "Bayes1," the μ_{iB} and d_k are assumed to have a normal prior distribution with mean 0 and variance 10000, a specification that is very vague (though still proper) and essentially treats them as distinct, fixed effects. For the standard deviation σ in a homogeneous random effects model, a Uniform (0.01, 2) prior is adopted. For the heterogeneous model, a more complex prior for σ_{Bk} is introduced; namely, we set $\log\sigma_{xy} = \log\sigma_0 + \upsilon_{xy}$, (x, y = 1, …, K) where $\sigma_0 \sim$ Uniform (0.01, 2), $\upsilon_{xy} \sim N(0, \psi^2)$, and ψ is a constant chosen to reflect a certain amount of heterogeneity among arms and we pick 0.347.[25] By adopting this prior, we can selectively estimate σ_{xy}; that is, we can obtain the posterior of σ_{xy} when there are data on the relation between two treatments, x and y, but our model does not provide (or require) the posterior of σ_{xy} when such data are not observed. For our inconsistency model, the w-factor has a $N(0, \sigma_w^2)$ where $\sigma_w \sim$ Uniform (0.01, 2). Here, the upper bound of uniform priors, 2, is large enough to be noninformative since a standard deviation for log odds ratio is very small.

Shrinkage Prior

Turning to the second prior ("Bayes2"), we introduce one more hierarchy for the baseline effect μ_{iB} to shrink toward the grand mean (m_B). Under this prior, the μ_{iB} are distributed $N(m_B, \tau^2)$, where the hyperparameters m_B and τ have N(0, 10000) and Uniform (0.01, 2) priors, respectively. Other parameters remain the same as in the noninformative prior case.

Model Selection

Regarding methods for Bayesian model choice, the Deviance Information Criterion (DIC) is a hierarchical modeling generalization of the familiar Akaike Information Criterion (AIC) often used in scenario like ours.[28] DIC can be calculated by summing , a measure of goodness of fit having a posterior predictive interpretation, and pD, an effective number of parameters capturing

overall model "size," a quantity inappropriately measured by AIC due to the presence of random effects. Smaller values of DIC correspond to preferred models. A DIC difference of five or more is generally regarded as practically meaningful.[27]

Decisionmaking

Probability of Being the Best Treatment

The primary goal of a multiple treatment comparison is to identify the best treatment. Suppose P_k is the marginal posterior probability of a particular event under treatment K, perhaps modeled with a logit function. Then if the event is a positive outcome we define the loss function as $T_k = P_k$ (and for negative outcome, we set $T_k = 1 - P_k$) so that a treatment with the smallest loss will be the best treatment. We then define the "Best1" probability as

$$\Pr\{\text{K is the best treatment} \mid \text{Data}\} = \Pr\{\text{rank}(T_k) = 1 \mid \text{Data}\}.$$

Probability of Being Among the Two Best Treatments

Similarly, one can calculate the probability of being the first or second best treatment, denoted by "Best12," by replacing the right hand side of the above equation with $\Pr\{\text{rank}(T_k) = 1 \text{ or } 2 \mid \text{Data}\}$, where small ranks indicate best treatments.

Frequentist Approach

Commercial software programs for frequentist multivariate random-effects meta-analyses have recently been developed, though they have some idiosyncrasies when handling multi-arm trials or incomparable baseline treatments.[29,30] We have the same binomial distribution for data as we defined above, and can fit a fixed effects model written as

$$\text{logit}(p_{ik}) = s_i + t_{k,}$$

where s_i is fixed study-specific effect for baseline treatment and t_k is the log odds ratio between drug k and baseline treatment with $t_1 = 0$.

For a random effects model, we can specify the logit model as follows:

$$\text{logit}(p_{ik}) = s_i + t_k + v_{ik,}$$

where the vector $\mathbf{v}_i$ of v_{ik} values has an independent multivariate normal distribution MVN($\mathbf{0}$,$\mathbf{\Omega}$), with K× K covariance matrix $\mathbf{\Omega}$. In SAS, we can fit this model using the GLIMMIX procedure with the assumption of $\mathbf{\Omega} = \sigma^2\mathbf{I}_k$, where $\mathbf{I}_k$ is K× K identity matrix, but this model is not recommended. Instead, we rewrite the random effects model as the context of Lu and Ades notation.[36] That is,

$$\text{logit}(p_{ik}) = \mu_i + \delta_{ik} - \qquad ,$$

where $\delta_{i1} = 1$ for all i and $(\delta_{i2,} \ldots, \delta_{iK})^T \sim \text{MVN}((d_2, \ldots, d_K)^T, \mathbf{\Sigma})$, with (K-1) × (K-1) covariance matrix $\mathbf{\Sigma}$. In this notation, we have $\mathbf{\Omega} = \mathbf{A\Sigma A}^T$, where $\mathbf{A}$ is a K × (K-1) matrix and the (i,j)th element of the $\mathbf{A}$ is $A_{ij} = I(i = j+1) - (1/K)$, where I denotes the indicator function. One can assign a certain structure for $\mathbf{\Sigma}$, but many authors recommend a simple structure such as homogeneous variance and 0.5 correlation across all arms. We refer to this model as the frequentist homogeneous random effects model. Please see Jones, et al.,[30] for details of the covariance matrix structure.

We can loosen the homogeneous variability assumption and fit a heterogeneous random effects model using a frequentist approach.[29] The model can be specified as $\text{logit}(p_{ik}) = \mu_i + \delta_{ik}$

with $\delta_{i1} = 0$ for all i, and $(\delta_{i2}, \ldots, \delta_{iK})^T \sim MVN((d_2, \ldots, d_K)^T, \boldsymbol{\Sigma})$. Here, $\boldsymbol{\Sigma}$ is a unstructured (K-1) × (K-1) covariance matrix. We can estimate $\boldsymbol{\Sigma}$ by likelihood based methods provided the data contain at least some information on every drug-by-drug relation. We can fit this model via Stata (Statistics/Data analysis, 12)[31] but, unfortunately, Stata cannot fit this model with our UI data since the data is too sparse to estimate all elements of the covariance matrix.

A final, rather crude tool for ranking treatments is the number needed to treat (NNT),[32] which is the expected number of patients required to achieve one event of the outcome using the pooled absolute risk difference.[33,34] Although we only use studies having placebo as the baseline arm to calculate NNT, this number is sometimes helpful to physicians in providing clinical understanding.

All of our Bayesian results were obtained from the WinBUGS software,[35] using 10000 Markov chain Monte Carlo (MCMC) samples after a 5000-sample algorithm burn-in. To check MCMC convergence, we used standard diagnostics, including trace plots and lag 1 sample autocorrelations. After discovering only mild lag 1 autocorrelations and attractive trace plots, we decided to use only a single MCMC chain, run for 5000 burn-in and 10000 production samples to save time. All frequentist calculations were performed using SAS 9.2 software to obtain maximum likelihood estimators with 95 percent confidence limits by using Gaussian quadrature approximation approach.[36]

Results

Tables 3–5 display the results of all eight Bayesian models (four models each with two possible priors; six Bayesian models for the continence outcome) and two frequentist models (fixed effect and homogeneous random effect models) for all seven pharmacological treatments in terms of continence, UI improvement, and discontinuation due to AE, respectively. Shown are estimated log odds ratios between treatment and placebo (d_k) with standard errors in parentheses from both frequentist and Bayesian methods, and the probability of being among the two best treatments (Best12) from the Bayesian analysis. For Bayesian analysis, we report the posterior median values. Note that the orders of d_k and Best12 probability are similar in Bayesian results. To find the best drug in terms of each outcome, we use d_k for frequentist methods and Best12 for Bayesian; NNT is also provided. The first part of all three tables provides Bayesian goodness-of-fit statistics. Table 4 reveals a decrease in the fit statistic between the fixed and random effects models; thus, introducing randomness among studies essentially forces improved model fit although the variability in the random effects (σ) is quite small. The heterogeneous random effects model yields almost the same DIC for all outcomes, and the homogeneous random effects model generally offers the best compromise between fit and complexity (i.e., lowest DIC); neither the addition of w-factors nor heterogeneous variances pay practically significant improvements in DIC. Regarding the two priors, again we see no meaningful difference in DIC, though the shrinkage prior is slightly preferred for the discontinuation outcome (Table 5). As such, for Bayesian decisionmaking, we adopt the homogeneous random effects models with the shrinkage prior.

In Table 3, there are no substantial differences in DIC across all Bayesian models and this might be due to small σ. The frequentist random effects model yields almost zero variability, resulting in the same d_k estimates between fixed and random effects models. In the Bayesian homogeneous random effects models, two priors provide slightly different order of d_k (propiverine moves to first place under the Bayes2 prior), but the Best12 probabilities deliver the same order and so does the frequentist ranking based on d_k, though there is the lack of statistically significant differences among the Best12 probabilities. Across all models, trospium is the best drug in terms of continence, suggesting the effect of trospium is dominant regardless of the presence of random effects or a shrinkage prior. Overall, trospium and propiverine appear to have a slight edge, with tolterodine appearing to be the worst drug to cure UI, given its smallest Best12 probabilities and d_k. The rankings based on NNT are rather different, with propiverine emerging as a clear winner, followed by a three-way tie for third place. However, we caution that few of the differences between drugs are statistically significant, a subject to which we return in Table 6.

Table 4 displays the results from frequentist and Bayesian models with respect to the UI improvement outcome. Again, frequentist random effects models give smaller σ estimates compared to Bayesian models. In the Bayesian results, propiverine has a greater than 0.7 probability of being the first or second best. The runner-up here appears to be oxybutynin, which emerges with the second highest probabilities of being among the top two. Tolterodine fares worst. Frequentist ranking based on d_k from random effects model gives the same results, though the drugs' differences are not statistically significant. NNT is not reported when the treatment fails to differ significantly from placebo; this is why trospium has no NNT. The estimated w-factors in the inconsistency model are small ($w_{137} = 0.00$ and $w_{147} = 0.20$), and there is no strong evidence of inconsistency.

Table 5 shows the model comparisons with respect to the safety outcome, discontinuation due to AE. Since the outcome now has a negative meaning, "Worst12" is now interpreted as being first or second worst. There is a roughly five unit decrease in DIC, resulting from a decrease in pD between the Bayes1 and Bayes2 priors across all models. In this specific dataset, the shrinkage encouraged by Bayes2 implies lower model complexity. All w-factors are smaller than 0.1, implying minimal inconsistency between direct and indirect comparisons. Again, the estimated σ from frequentist homogeneous random effects model is close to zero. In both frequentist and Bayesian analyses, oxybutynin is the worst drug with the highest d_k and Worst12 probability from all models, followed by fesoterodine. tolterodine has the smallest d_k and 0 probability of being the first or second least safe drug, suggesting it is safest among the seven treatments. Although the Worst12 probabilities are not significant between drugs, the Bayes2 prior gives slightly smaller standard deviation of Worst12 (see oxybutynin) than the Bayes1 prior. Here, smaller NNT values mean *less* safe; e.g., an NNT of 24 means that we would expect that one woman of each 24 enrolled would not tolerate treatment.

Figure 2 shows our findings graphically in terms of odds ratios with MCMC-computed 95 percent equal-tail credible intervals from Bayesian models, or 95 percent confidence intervals from frequentist models for each outcome. We compare four models; Bayes2 fixed effects model, frequentist random effects model, and Bayes1 and 2 homogeneous random effects models. We mark the best drug with respect to each outcome with a triangle character, and the worst drug with a square. For the continence outcome, all of the odds ratios are significantly greater than 0 (that is, all drugs are more effective than placebo) and trospium and propiverine have odds ratios close to 2, meaning that being treated with either of these leads to about two times greater odds of continence compared to being untreated. However there appear to be no significant differences between drugs. Regarding the UI improvement outcome, the odds ratios of propiverine, oxybutynin, and solifenacin exceed 2, while tolterodine delivers the worst performance, though they are not significantly different. In the discontinuation outcome, tolterodine is the safest drug and oxybutynin performs worst. There are just two significant differences between drugs: tolterodine versus oxybutynin and fesoterodine (their 95 percent intervals do not overlap). Note that propiverine emerges as having very wide intervals because there are only two studies for this drug, and the two studies do not agree with the direction of this drug's safety.

Table 6 presents odds ratios and 95 percent credible or confidence intervals for all pairwise comparisons under both our Bayesian analyses (Bayes1 and Bayes2) and a frequentist analysis carried out with the homogeneous random effects model. Although most drugs are significantly effective compared to placebo with all outcomes, there is only one significant odds ratio between active drugs (tolterodine vs. trospium) for the continence outcome, two for the UI improvement outcome (oxybutynin and propiverine vs. tolterodine), and three for the discontinuation AE outcome (tolterodine vs. fesoterodine and oxybutynin and trospium vs. oxybutynin) under the Bayes1 (noninformative) prior. The Bayes2 prior gives similar significances. The Bayesian analyses generally give wider 95 percent credible intervals than the frequentist method because the Bayesian approach incorporates all sources of uncertainty into the model. However, note that Bayes2 does sometimes find significance where the frequentist method does not; e.g., darifenacin versus fesoterodine for discontinuation due to AE.

Figure 3 exhibits rankings according to two pairs of outcomes under the Bayes2 homogeneous random effects model.[37] Drugs plotted at the upper right corner are considered the best in terms of both efficacy and safety. Panel (a) compares continence and discontinuation

outcomes. While this display does not include standard errors (and thus the significance of the differences shown is difficult to judge), trospium emerges as most attractive since it is the best in terms of continence and also the third safest drug (although it fails to differ from placebo in terms of UI improvement under the Bayes2 homogeneous random effects model, it is very close and significant in the other models). Panel (b) indicates solifenacin may offer the best compromise between the UI improvement and discontinuation outcomes. This drug delivers the third best outcome for UI improvement and a Worst12 probability of 0.026, fairly small though the discontinuation ranking is rather high at 5. As such, these two drugs may be viewed (at least informally) as offering the best compromise between safety and efficacy in this investigation. In summary, while frequentist and Bayesian analyses produce broadly comparable odds ratios of safety and efficacy, the Bayesian method's ability to deliver the probability that any treatment is among the top two such treatments leads to more meaningful clinical interpretation.

Discussion

The main objective of this report has been to compare methodologies between frequentist and Bayesian, rather than offer a full comparative clinical assessment. Our results indicate that Bayesian methods are more flexible than frequentist methods, as well as providing substantially more information useful for clinicians and health policymakers. Theoretically, Bayesian methods are appealing due to their more rigorous mathematical foundation and their ability to incorporate all available sources of information in a model-based framework, rather than simply attempt to combine p-values in some way. From a more practical point of view, Bayesian methods offer direct probability statements about patient-centered outcome variables, such as the probability that one drug is the best or among the top two drugs for an indication, or the probability of experiencing a particular endpoint given the patient takes a particular drug. By contrast, frequentist analyses rely on traditional notions of statistical significance, and therefore do not provide an estimate of the probability of being the best drug. The Bayesian methods remedy this shortcoming, leading to more practical recommendations, though we caution that the ranks shown in Figure 3 do not come with associated standard errors, and so judging the significance of the differences between drugs must come from the log-odds ratios and Best12 probabilities in Tables 3–5.

Thanks to methodological and computational development in frequentist MTCs, we can fit frequentist fixed and random effects models comparable to Bayesian models. However, there are some limitations in the frequentist analysis. Handling study arms with zero events is always problematic, and our UI data contain such studies. One can augment the data by adding one individual with 0.5 successes to an arm containing zero events, or simply exclude studies with no events at all, but both methods have potentially harmful impacts on asymptotic approximations. When we fit the heterogeneous random effects model in Stata, we have to manipulate the dataset to make all studies have the same baseline treatment (say, placebo) by including 0.01 artificial individuals and 0.001 artificial successes for the missing placebo arms. Also, when we have sparse data, we cannot fit this model since there is not enough information to estimate all the elements of the unstructured covariance matrix, while the Bayesian method remains feasible since it does not include any inestimable elements of the covariance matrix. To measure inconsistency, the cross-validation method is used in frequentist analysis; i.e., we can estimate log odds ratios from studies including direct comparisons and indirect comparisons separately, and compare these quantities. However, Bayesian analysis allows us to measure the amount of inconsistency statistically with w-factors. In frequentist analysis, the estimates of random effect variability, σ, are always smaller than in Bayesian analysis (in the UI data analysis, σ for continence and discontinuation outcomes are close to zero). Also, the standard errors of the log odds ratios are slightly smaller than from Bayesian models, leading to more conservative conclusions. These findings are similar the those of Jones, et al.[30]

In the specific context of our UI data, both frequentist and Bayesian meta-analyses conclude that most of the drugs were better than placebo in achieving continence and improving UI. Differences in efficacy among the drugs are often insignificant, but the Bayesian probabilities of being among the top two most efficacious (or safest) drugs may be of practical import. Even though our Bayesian and frequentist odds ratios do not show many statistically significant differences between study drugs in the odds of continence or improving UI, we are able to identify the drugs that are more efficacious, as well as those having the highest odds of discontinuation due to adverse effects. Combining these sets of results enables an informed decision as to which drugs should be used, based on a joint assessment of their probabilities of

being the most effective and safest. Of course, a sensible threshold for the probability for being the most effective and safe drug may vary depending on the topic and the appropriateness of the model and prior, which may of course be checked statistically. For example, although drugs can be ranked based on Best12 probabilities, the differences between drugs in terms of other parameters such as log odds ratio could be very small, and the ranking can thus be overinterpreted.

Both our Bayesian and frequentist analyses utilized random effects, and thus avoided the assumption of common drugs' effect sizes across trials. Clinicians and patients need to know rates of the benefits and harms to make informed decisions. The NNTs derived from frequentist analyses provide useful information for clinicians, but their interpretation is often difficult for patients. Bayesian analysis provides an intuitively appealing probability of the outcome that easily leads to identifying the best and the worst treatment for each measure of benefit or harm. A single estimate of the balance between benefits and harms would be the most simple and useful information for making informed decisions in clinical settings. Also, when there are multiple outcomes (as in the UI data), we could choose sensible weights for each outcome to find the best compromising drug in terms of one's preference (i.e., a clinician might well put more weight on the safety outcome.

Although Bayesian methods provide many promising features, we can still improve our analysis. In this analysis, we only consider noninformative and shrinkage priors. While our shrinkage prior is partially informative, we do not incorporate specific prior information regarding efficacy or safety for any drug due to limited information about natural history of urgency UI. We could construct informative priors based upon either external data or expert opinion, possibly leading to better model fitting. For decision making, Best12 probabilities are used to find the best drug with respect to each outcome, but one could set up other metrics to evaluate drug performance, and the Bayesian framework can easily handle this. Also, we encourage comprehensive conclusions based on various tools, not solely based on Best12 probabilities from a single model. For example, a drug could be a winner in terms of Best12, but its odds ratio may not imply significant differences from other drugs.

Our study itself has several limitations. We assume patients assigned to different drugs across studies have similar baseline characteristics, so the potential impact of differential baselines could exist. Also, we do not adjust for study quality (say, due to difference in randomization methods or publication bias), role of the drug within the RTCs, doses of the drugs, age of the women, their baseline UI severities, or their natural histories of urgency UI. Meta-regression is one of methods to incorporate those study-level characteristics, and we hope to apply this method in a future manuscript. Differentiation between immediate release (IR) and extended release (ER) formulations could also change our findings, but we lack sufficient data to estimate this effect.

Regarding the definition of UI improvement, although our studies have various definitions of UI improvement potentially leading to clinical heterogeneity, our random effects models, handling heterogeneity between studies, imply small study-to-study variability. We analyzed how differences in definitions of improved UI can influence the treatment effects, but found them likely to be small. For instance, the studies that defined improvement as a reduction of 75 percent in UI episodes (instead of 50 percent) lead to similar relative risks and absolute risk differences. Our choice of the safety endpoint (discontinuation due to AE) could be problematic because the definitions could be widely different among study protocols. We also do not analyze all available adverse effects from the drugs, such as dry mouth or constipation. Patients may

have differential sensitivity to specific adverse events, but to estimate this individualized effect, *patient-level* data with individual-level covariates are required.

Broad recommendations regarding choice among Bayesian and frequentist models await simulation studies where performance and rankings of the methods can be compared in various settings where the true states of nature (say, that the indirect evidence is inconsistent with the direct) are known. Finally, fully Bayesian methods for formally combining both efficacy and safety data into a single decision rule would be a significant aid in making a sensible overall decision. We hope to address these and other methodological issues in a future publication.

Table 1. Definitions of urinary incontinence and treatment outcomes

Outcomes	Definition
Continence	Absence of any involuntary leakage of urine Author's reports of cure, absence of incontinent episodes in bladder diaries, negative pad stress, or no abnormalities noted on urodynamics
Improvement in UI	Reduction frequency and severity of incontinence episodes by >50% Reduction in pad stress test by >50% Reduction in restrictions of daily activities due to incontinence Women's perception of improvement in their bladder condition
Discontinuation of treatment due to adverse effect	Subject refusal to continue treatment due to adverse effects or physician decision to withdraw treatment due to adverse effects

Table 2. Raw UI data

Study	placebo	darifenacin	fesoterodine	oxybutynin	propiverine	solifenacin	tolterodine	trospium
Kaplan, 2010[38]	258, 287, 10; 480		609, 709, 48; 963				566, 654, 29; 974	
NCT00444925[39]	138, 32, 6; 337		396, 102, 44; 685				358, 79, 28; 690	
Junemann, 2006[40]	77, 94, 1; 202				211, 264, 11; 391			
Zinner, 2004[41]	29, 141, 15; 261							55, 186, 23; 262
Goode, 2004 [42]	8, 18, N; 65			15, 33, N; 67				
Moore, 1990[43]	0, 1, N;25			5, 10, N;28				
Dorschner, 2000[44]	15, 11, N; 49				24, 19, N; 49			
Vardy, 2009[45]	36, 109, N;382					48, 196, N;386		
Staskin, 2009[46]	69, N, 13;400			108, N, 19;389				
Chu, 2009[47]	80, N, 18;332					119, N, 37;340		
Cardozo, 2006[48]	266, N, 40; 781					405, N, 51; 778		
Staskin, 2006[49]	122, N, 19; 430					184, N, 31; 452		
Karram, 2009[50]	93, N, 17;367					133, N, 24;372		
Sand, 2009[51]	103, N, 18;505							163, N, 24;484
Staskin, 2007[52]	34, N, 11;303							61, N, 12;298
Herschorn, 2010[53]	N, 113, 6;334		N, 293, 44;679				N, 256, 28;684	
Homma, 2003[54]	N, 31, 11;122			N, 129, 42;244			N, 100, N;239	
Abrams, 1998[55]	N, 27, 7;57			N, 58, 20;118			N, 59, 10;118	
Steers, 2005[56]	N, 60, 4;127, 41	N, 160, 6;268, 160						
Hill, 2006[57]	N, 15, 3;109	N, 28, 2;108						
Chapple, 2007[58]	N, 47, 9;133	N, 122, 12;266						
Dmochowski, 2010[59]	N, 137, 21;445		N, 182, 34;438					
Thuroff, 1991[60]	N, 15, 0;52			N, 26, 2;63				

Table 2. Raw UI data (continued)

Study	placebo	darifenacin	fesoterodine	oxybutynin	propiverine	solifenacin	tolterodine	trospium
Herschorn, 2008[61]	N, 64, 2;207						N, 156, 12;410	
Lee, 2002[62]				N, 53, 18; 116			N, 50, 11; 112	
Lehtoranta, 2002[63]	2, N, N; 9			4, N, N; 9				
Rogers, 2008[64]	89, N, N;211						115, N, N;202	
Malone-Lee, 2009[65]	26, N, N;142						41, N, N;165	
Dmochowski, 2008[66]	58, N, N; 284							95, N, N; 280
Sand, 2009[67]	N, 167, N;430		N, 291, N;452				N, 140, N;227	
Madersbacher, 1999[68]	N, 43, N;72			N, 116, N;145				
Johnson, 2005[69]	N, 1, N;38			N, 4, N;46				
Wang, 2006[70]	N, 0, N;21			N, 2, N;23				
Szonyi, 1995[71]	N, 16, N;29			N, 22, N;28				
Lee, 2010[72]	N, 12, N;88				N, 55, N;176			
Toglia, 2009[73]	N, 206, N;367					N, 260, N;372		
Kelleher, 2002[74]	N, 218, N;508						N, 294, N;507	
Rogers, 2009[75]	N, 58, N;211						N, 79, N;202	
Staskin, 2004[76]	N, 8, N;326							N, 5, N;327
Zinner, 2005[77]	N, N, 0;19	N, N, 1;19		N, N, 4;19				
Chapple, 2007[78]	N, N, 6;285		N, N, 14;288				N, N, 9;290	
Drutz, 1999[79]	N, N, 4; 56			N, N, 23;112			N, N, 7; 109	
Yamaguchi, 2007[80]	N, N, 11;406				N, N, 26;402	N, N, 26;385		
Chapple, 2004[81]	N, N, 10;267					N, N, 7;269	N, N, 5;266	
Chapple, 2004[82]	N, N, 2;164	N, N, 3;229						
Zinner, 2006[83]	N, N, 10;225	N, N, 17;214						
U.S. Food and Drug Administration, 2004[84,85]	N, N, 4;115	N, N, 8;112						
U.S. Food and Drug Administration, 2004[84,85]	N, N, 3;164	N, N, 3;115						
Chapple,2004[86]	N, N, 7;183		N, N, 22;186					
Cardozo, 2008[87]	N, N, 4;224					N, N, 15;641		

Table 2. Raw UI data (continued)

Study	placebo	darifenacin	fesoterodine	oxybutynin	propiverine	solifenacin	tolterodine	trospium
Rentzhog, 1998[88]	N, N, 3;13						N, N, 2;67	
Malone-Lee, 2001[89]	N, N, 1;74						N, N, 7;73	
Jacquetin, 2001[90]	N, N, 1;51						N, N, 2;103	
Khullar, 2004[91]	N, N, 16;285						N, N, 26;569	
Rudy, 2006 [92]	N, N, 15;329							N, N, 24;329
U.S. Food and Drug Administration, 2007[93,94]	N, N, 8;284							N, N, 18;280
U.S. Food and Drug Administration, 2007[93,94]	N, N, 11;303							N, N, 12;298
Chapple, 2005[95]		N, N, 1;13		N, N, 2;12				
Appell, 2001[96]				N, N, 14; 185			N, N, 15; 193	
Armstrong, 2005[97]				N, N, 20;391			N, N, 19;399	
Appell, 1997[98]				N, N, 70;349			N, N, 2;121	
Zellner, 2009[99]				N, N, 61;830				N, N, 47;828
Halaska, 2003[100]				N, N, 3;90				N, N, 4;267
Pharmaceutical Research and Manufacturers of America[101]						N, N, 25;593	N, N, 23;607	
Choo, 2008[102]						N, N, 7;119	N, N, 2;118	

Note: Each cell lists counts for 'continence, UI improvement, discontinuation of the study; sample size', with 'N' indicating no response in that category.

Table 3. Bayesian and frequentist model comparisons for UI pharmacological treatments with outcome continence

		Fixed Effects Frequentist	Fixed Effects Bayes1	Fixed Effects Bayes2	Random Effects Homogeneous Frequentist	Random Effects Homogeneous Bayes1	Random Effects Homogeneous Bayes2	Random Effects Heterogeneous Bayes1	Random Effects Heterogeneous Bayes2
DIC			284.8	283.9		286.4	285.1	286.8	285.4
Dbar			259.7	259.7		258.2	258.3	258.6	258.5
pD			25.1	24.2		28.2	26.8	28.2	26.9
	NNT	**Log odds ratio (d_k)**							
darifenacin	NA	NA	NA	NA	NA	NA	NA	NA	NA
fesoterodine	8	0.547 (0.08)	0.549 (0.08)	0.564 (0.08)	0.547 (0.08)	0.562 (0.11)	0.573 (0.11)	0.564 (0.11)	0.572 (0.11)
oxybutynin	9	0.677 (0.16)	0.686 (0.16)	0.624 (0.16)	0.677 (0.16)	0.678 (0.17)	0.584 (0.18)	0.691 (0.18)	0.605 (0.19)
propiverine	6	0.664 (0.16)	0.675 (0.16)	0.699 (0.16)	0.664 (0.16)	0.650 (0.20)	0.702 (0.18)	0.674 (0.19)	0.686 (0.18)
solifenacin	9	0.597 (0.07)	0.597 (0.06)	0.596 (0.07)	0.597 (0.07)	0.580 (0.08)	0.582 (0.08)	0.585 (0.09)	0.575 (0.08)
tolterodine	12	0.338 (0.08)	0.341 (0.07)	0.356 (0.08)	0.338 (0.08)	0.362 (0.09)	0.368 (0.09)	0.360 (0.10)	0.361 (0.09)
trospium	9	0.702 (0.10)	0.702 (0.10)	0.683 (0.10)	0.702 (0.10)	0.707 (0.11)	0.690 (0.11)	0.697 (0.11)	0.703 (0.10)
σ					0.00	0.08	0.07		
Best12									
placebo			0.000 (0.00)	0.000 (0.00)		0.000 (0.00)	0.000 (0.00)	0.000 (0.00)	0.000 (0.00)
darifenacin			NA	NA		NA	NA	NA	NA
fesoterodine			0.083 (0.28)	0.141 (0.35)		0.152 (0.36)	0.214 (0.41)	0.167 (0.37)	0.184 (0.39)
oxybutynin			0.560 (0.50)	0.409 (0.49)		0.548 (0.50)	0.344 (0.47)	0.564 (0.50)	0.391 (0.49)
propiverine			0.523 (0.50)	0.614 (0.49)		0.471 (0.50)	0.615 (0.49)	0.503 (0.50)	0.583 (0.49)
solifenacin			0.177 (0.38)	0.203 (0.40)		0.173 (0.38)	0.175 (0.38)	0.152 (0.36)	0.161 (0.37)
tolterodine			0.000 (0.00)	0.000 (0.00)		0.002 (0.04)	0.002 (0.04)	0.002 (0.05)	0.002 (0.04)
trospium			0.658 (0.47)	0.633 (0.48)		0.654 (0.48)	0.651 (0.48)	0.612 (0.49)	0.679 (0.47)

Table 4. Bayesian and frequentist model comparisons for UI pharmacological treatments with outcome UI improvement

		Fixed Effects Frequentist	Fixed Effects Bayes1	Fixed Effects Bayes2	Random Effects Homo-geneous Frequentist	Random Effects Homo-geneous Bayes1	Random Effects Homo-geneous Bayes2	Random Effects Hetero-geneous Bayes1	Random Effects Hetero-geneous Bayes2	Random Effects Homo-geneous W-Factors Bayes1	Random Effects Homo-geneous W-Factors Bayes2
DIC			440.8	440.5		434.5	433.5	434.1	433.7	434.3	433.5
Dbar			405.7	406.0		388.9	388.6	389.0	388.4	388.4	388.2
pD			35.1	34.5		45.6	44.9	45.1	45.3	45.9	45.3
	NNT	**Log odds ratio (d_k)**									
darifenacin	9	0.523 (0.14)	0.528 (0.14)	0.533 (0.14)	0.527 (0.15)	0.538 (0.19)	0.540 (0.18)	0.536 (0.18)	0.554 (0.19)	0.533 (0.18)	0.536 (0.18)
fesoterodine	10	0.678 (0.06)	0.681 (0.06)	0.682 (0.06)	0.670 (0.07)	0.670 (0.10)	0.665 (0.10)	0.677 (0.10)	0.672 (0.11)	0.663 (0.10)	0.663 (0.10)
oxybutynin	6	0.800 (0.11)	0.806 (0.11)	0.792 (0.10)	0.804 (0.11)	0.819 (0.13)	0.803 (0.13)	0.820 (0.13)	0.785 (0.13)	0.848 (0.14)	0.827 (0.14)
propiverine	5	0.896 (0.15)	0.898 (0.15)	0.896 (0.15)	0.899 (0.17)	0.909 (0.20)	0.894 (0.19)	0.895 (0.20)	0.901 (0.20)	0.902 (0.20)	0.906 (0.20)
solifenacin	6	0.777 (0.11)	0.775 (0.11)	0.784 (0.11)	0.775 (0.13)	0.776 (0.17)	0.781 (0.17)	0.779 (0.18)	0.788 (0.19)	0.771 (0.17)	0.779 (0.17)
tolterodine	10	0.452 (0.05)	0.454 (0.05)	0.454 (0.05)	0.460 (0.06)	0.470 (0.09)	0.466 (0.09)	0.468 (0.08)	0.463 (0.08)	0.460 (0.08)	0.458 (0.08)
trospium	.	0.618 (0.17)	0.628 (0.18)	0.586 (0.17)	0.590 (0.20)	0.552 (0.24)	0.499 (0.24)	0.554 (0.27)	0.485 (0.30)	0.545 (0.24)	0.492 (0.24)
σ					0.10	0.17	0.18			0.18	0.17
Best12											
placebo			0.000 (0.00)	0.000 (0.00)		0.000 (0.00)	0.000 (0.00)	0.000 (0.00)	0.000 (0.00)	0.000 (0.00)	0.000 (0.00)
darifenacin			0.031 (0.17)	0.031 (0.17)		0.072 (0.26)	0.070 (0.25)	0.060 (0.24)	0.089 (0.28)	0.052 (0.22)	0.063 (0.24)
fesoterodine			0.054 (0.23)	0.058 (0.23)		0.096 (0.29)	0.103 (0.30)	0.112 (0.32)	0.127 (0.33)	0.080 (0.27)	0.088 (0.28)
oxybutynin			0.556 (0.50)	0.519 (0.50)		0.571 (0.49)	0.545 (0.50)	0.547 (0.50)	0.466 (0.50)	0.634 (0.48)	0.602 (0.49)
propiverine			0.779 (0.41)	0.792 (0.41)		0.721 (0.45)	0.725 (0.45)	0.710 (0.45)	0.726 (0.45)	0.723 (0.45)	0.730 (0.44)
solifenacin			0.430 (0.50)	0.489 (0.50)		0.424 (0.49)	0.474 (0.50)	0.439 (0.50)	0.494 (0.50)	0.396 (0.49)	0.445 (0.50)
tolterodine			0.000 (0.00)	0.000 (0.00)		0.000 (0.02)	0.001 (0.08)	0.001 (0.02)	0.001 (0.02)	0.001 (0.02)	0.001 (0.03)
Trospium			0.151 (0.36)	0.112 (0.32)		0.116 (0.32)	0.083 (0.28)	0.131 (0.34)	0.098 (0.30)	0.114 (0.32)	0.072 (0.26)

Table 5. Bayesian and frequentist model comparisons for UI pharmacological treatments with outcome discontinuation due to AE

		Fixed Effects Frequentist	Fixed Effects Bayes1	Fixed Effects Bayes2	Random Effects Homo-geneous Frequentist	Random Effects Homo-geneous Bayes1	Random Effects Homo-geneous Bayes2	Random Effects Hetero-geneous Bayes1	Random Effects Hetero-geneous Bayes2	Random Effects Homo-geneous W-Factors Bayes1	Random Effects Homo-geneous W-Factors Bayes2
DIC			601.2	594.8		598.6	593.3	596.7	591.1	600.3	594.4
Dbar			547.5	549.0		531.8	536.9	529.5	534.0	531.2	537.0
pD			53.7	45.8		66.8	56.4	67.2	57.1	69.1	57.4
	NNT	**Log odds ratio (d_k)**									
darifenacin	.	0.316 (0.21)	0.323 (0.21)	0.323 (0.19)	0.316 (0.21)	0.317 (0.23)	0.282 (0.21)	0.310 (0.25)	0.311 (0.21)	0.310 (0.24)	0.317 (0.21)
fesoterodine	34	0.797 (0.13)	0.801 (0.13)	0.785 (0.12)	0.797 (0.13)	0.838 (0.17)	0.794 (0.15)	0.815 (0.16)	0.794 (0.15)	0.850 (0.17)	0.777 (0.16)
oxybutynin	24	0.841 (0.13)	0.843 (0.13)	0.908 (0.12)	0.841 (0.13)	0.870 (0.17)	0.924 (0.16)	0.871 (0.17)	0.949 (0.16)	0.884 (0.21)	0.971 (0.18)
propiverine	38	0.698 (0.25)	0.698 (0.26)	0.544 (0.24)	0.699 (0.25)	0.762 (0.34)	0.531 (0.30)	0.734 (0.34)	0.565 (0.30)	0.755 (0.35)	0.525 (0.29)
solifenacin	.	0.470 (0.11)	0.466 (0.11)	0.457 (0.11)	0.470 (0.11)	0.488 (0.15)	0.453 (0.14)	0.489 (0.15)	0.469 (0.13)	0.489 (0.16)	0.451 (0.15)
tolterodine	.	0.203 (0.11)	0.206 (0.11)	0.214 (0.10)	0.203 (0.11)	0.210 (0.14)	0.203 (0.12)	0.208 (0.13)	0.206 (0.13)	0.219 (0.15)	0.199 (0.13)
trospium	59	0.453 (0.13)	0.451 (0.13)	0.453 (0.12)	0.453 (0.13)	0.435 (0.18)	0.428 (0.15)	0.441 (0.16)	0.442 (0.15)	0.430 (0.18)	0.436 (0.16)
Σ					0.00	0.25	0.22			0.27	0.22

Table 5. Bayesian and frequentist model comparisons for UI pharmacological treatments with outcome discontinuation due to AE (continued)

		Fixed Effects Frequentist	Fixed Effects Bayes1	Fixed Effects Bayes2	Random Effects Homo-geneous Frequentist	Random Effects Homo-geneous Bayes1	Random Effects Homo-geneous Bayes2	Random Effects Hetero-geneous Bayes1	Random Effects Hetero-geneous Bayes2	Random Effects Homo-geneous W-Factors Bayes1	Random Effects Homo-geneous W-Factors Bayes2
Worst12											
placebo			0.000 (0.00)	0.000 (0.00)		0.000 (0.00)	0.000 (0.00)	0.000 (0.00)	0.000 (0.00)	0.000 (0.00)	0.000 (0.00)
darifenacin			0.024 (0.15)	0.010 (0.10)		0.029 (0.17)	0.014 (0.12)	0.023 (0.15)	0.013 (0.11)	0.020 (0.14)	0.023 (0.15)
fesoterodine			0.715 (0.45)	0.820 (0.38)		0.683 (0.47)	0.777 (0.42)	0.668 (0.47)	0.747 (0.44)	0.685 (0.46)	0.755 (0.43)
oxybutynin			0.828 (0.38)	0.967 (0.18)		0.758 (0.43)	0.944 (0.23)	0.803 (0.40)	0.948 (0.22)	0.757 (0.43)	0.959 (0.20)
propiverine			0.416 (0.49)	0.183 (0.39)		0.484 (0.50)	0.216 (0.41)	0.456 (0.50)	0.245 (0.43)	0.481 (0.50)	0.206 (0.40)
solifenacin			0.008 (0.09)	0.008 (0.09)		0.023 (0.15)	0.026 (0.16)	0.027 (0.16)	0.023 (0.15)	0.032 (0.18)	0.026 (0.16)
tolterodine			0.000 (0.00)	0.000 (0.00)		0.000 (0.00)	0.000 (0.00)	0.000 (0.01)	0.000 (0.00)	0.000 (0.00)	0.000 (0.00)
trospium			0.010 (0.10)	0.013 (0.11)		0.024 (0.15)	0.023 (0.15)	0.021 (0.14)	0.025 (0.16)	0.026 (0.16)	0.032 (0.17)

Table 6. Odds ratios and 95% confidence or credible intervals of pairwise comparisons among frequentist, Bayes1, and Bayes2 under homogeneous random effects model

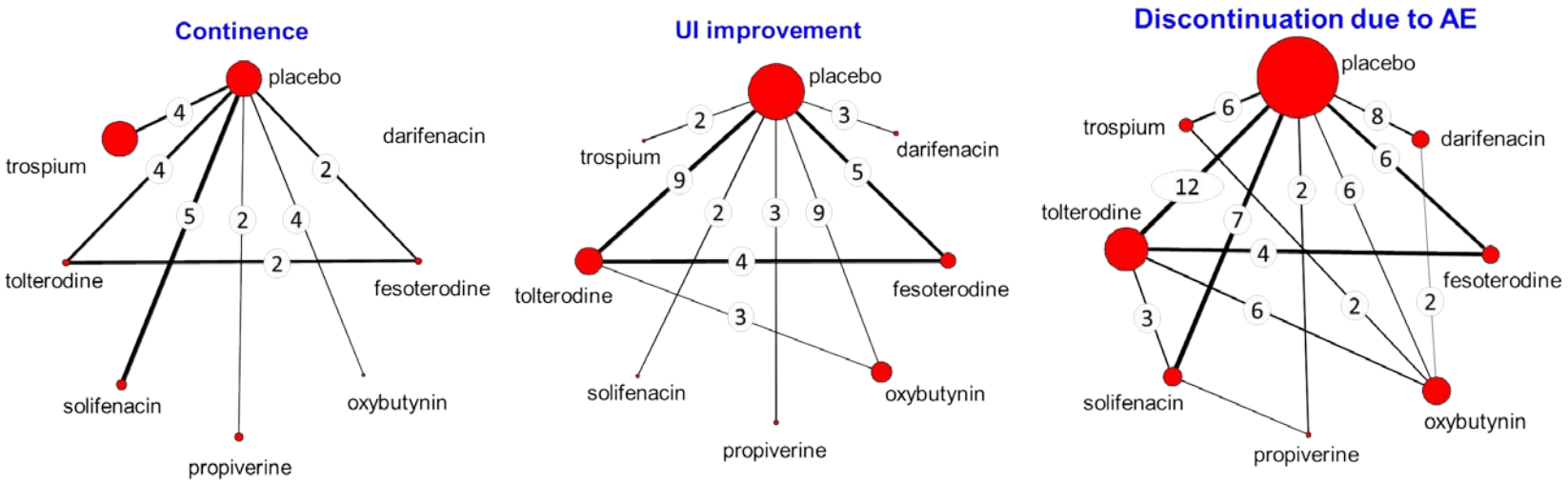
Active (control)	Continence Frequentist	Continence Bayes1	Continence Bayes2	UI Improvement Frequentist	UI Improvement Bayes1	UI Improvement Bayes2	Discontinuation Due to AE Frequentist	Discontinuation Due to AE Bayes1	Discontinuation Due to AE Bayes2
fesoterodine (darifenacin)				1.15 (0.82 - 1.62)	1.14 (0.75 - 1.72)	1.13 (0.76 -1.69)	1.62 (1.00 - 2.62)	1.69 (0.95 - 3.01)	**1.67 (1.02 - 2.72)**
oxybutynin (darifenacin)				1.32 (0.90 - 1.92)	1.33 (0.85 - 2.08)	1.30 (0.84 - 2.00)	**1.69 (1.05 - 2.73)**	1.75 (0.97 - 2.98)	**1.91 (1.18 - 3.13)**
propiverine (darifenacin)				1.45 (0.93 - 2.27)	1.45 (0.85 - 2.50)	1.42 (0.83 - 2.41)	1.47 (0.77 - 2.81)	1.56 (0.74 - 3.66)	1.30 (0.63 - 2.56)
solifenacin (darifenacin)				1.28 (0.86 - 1.91)	1.27 (0.76 - 2.09)	1.28 (0.78 - 2.07)	1.17 (0.73 - 1.87)	1.19 (0.68 - 2.04)	1.19 (0.74 - 1.89)
tolterodine (darifenacin)				0.94 (0.67 - 1.30)	0.94 (0.63 - 1.39)	0.93 (0.63 - 1.37)	0.89 (0.56 - 1.43)	0.90 (0.52 - 1.48)	0.92 (0.59 - 1.46)
trospium (darifenacin)				1.06 (0.65 - 1.75)	1.02 (0.55 - 1.79)	0.96 (0.51 - 1.67)	1.15 (0.71 - 1.86)	1.13 (0.62 - 1.97)	1.15 (0.69 - 1.91)
oxybutynin (fesoterodine)	1.14 (0.80 - 1.62)	1.13 (0.77- 1.72)	1.02 (0.68 - 1.57)	1.14 (0.89 - 1.47)	1.16 (0.87 - 1.57)	1.15 (0.84 - 1.56)	1.05 (0.77 - 1.43)	1.03 (0.69 - 1.60)	1.14 (0.79 - 1.69)
propiverine (fesoterodine)	1.12 (0.79 - 1.61)	1.09 (0.73 - 1.73)	1.14 (0.76 - 1.72)	1.26 (0.88 - 1.80)	1.27 (0.82 - 2.01)	1.26 (0.82 - 1.94)	0.91 (0.52 - 1.57)	0.93 (0.45 - 2.00)	0.77 (0.40 - 1.49)
solifenacin (fesoterodine)	1.05 (0.86 - 1.29)	1.02 (0.77 - 1.32)	1.01 (0.76 - 1.30)	1.11 (0.83 - 1.49)	1.11 (0.75 - 1.66)	1.12 (0.76 - 1.69)	0.72 (0.53 - 0.99)	0.70 (0.45 - 1.10)	0.71 (0.49 - 1.05)
tolterodine (fesoterodine)	**0.81 (0.71 - 0.93)**	0.82 (0.64 - 1.00)	**0.81 (0.67 - 0.98)**	**0.81 (0.70 - 0.94)**	0.82 (0.67 - 1.01)	0.82 (0.67 - 1.01)	**0.55 (0.44 - 0.70)**	**0.53 (0.38 - 0.74)**	**0.55 (0.41 - 0.76)**
trospium (fesoterodine)	1.17 (0.91 - 1.50)	1.16 (0.84 - 1.56)	1.13 (0.83 - 1.52)	0.92 (0.61 - 1.40)	0.89 (0.52 - 1.45)	0.85 (0.49 - 1.34)	**0.71 (0.51 - 1.00)**	0.67 (0.41 - 1.08)	0.70 (0.45 - 1.04)
propiverine (oxybutynin)	0.99 (0.63 - 1.54)	0.98 (0.57 - 1.60)	1.12 (0.66 - 1.78)	1.10 (0.74 - 1.63)	1.08 (0.68 - 1.78)	1.10 (0.69 - 1.73)	0.87 (0.50 - 1.51)	0.91 (0.44 - 1.92)	0.67 (0.35 - 1.34)
solifenacin (oxybutynin)	0.92 (0.66 - 1.30)	0.90 (0.59 - 1.30)	0.99 (0.65 - 1.39)	0.97 (0.69 - 1.37)	0.95 (0.62 - 1.47)	0.98 (0.64 - 1.52)	**0.69 (0.50 - 0.95)**	0.69 (0.44 - 1.02)	**0.62 (0.42 - 0.93)**
tolterodine (oxybutynin)	0.71 (0.50 - 1.01)	0.73 (0.48 - 1.05)	0.80 (0.52 - 1.16)	**0.71 (0.57 - 0.89)**	**0.70 (0.54 - 0.91)**	**0.71 (0.55 - 0.93)**	**0.53 (0.41 - 0.68)**	**0.52 (0.37 - 0.70)**	**0.49 (0.36 - 0.65)**
trospium (oxybutynin)	1.03 (0.71 - 1.48)	1.03 (0.64 - 1.52)	1.11 (0.72 - 1.63)	0.81 (0.51 - 1.27)	0.77 (0.43 - 1.26)	0.73 (0.41 - 1.23)	**0.68 (0.51 - 0.90)**	**0.65 (0.42 - 0.95)**	**0.61 (0.42 - 0.86)**
solifenacin (propiverine)	0.94 (0.66 - 1.32)	0.93 (0.61 - 1.40)	0.88 (0.59 - 1.28)	0.88 (0.58 - 1.34)	0.87 (0.52 - 1.48)	0.90 (0.54 - 1.51)	0.80 (0.49 - 1.30)	0.76 (0.37 - 1.44)	0.92 (0.50 - 1.69)
tolterodine (propiverine)	0.72 (0.51 - 1.03)	0.75 (0.49 - 1.12)	0.72 (0.48 - 1.05)	**0.65 (0.45 - 0.92)**	**0.65 (0.41 - 0.98)**	**0.65 (0.43 - 1.00)**	0.61 (0.36 - 1.04)	0.57 (0.27 - 1.13)	0.72 (0.39 - 1.35)

Table 6. Odds ratios and 95% confidence or credible intervals of pairwise comparisons among frequentist, Bayes1, and Bayes2 under homogeneous random effects model (continued)

Active (control)	Continence Frequentist	Continence Bayes1	Continence Bayes2	UI Improvement Frequentist	UI Improvement Bayes1	UI Improvement Bayes2	Discontinuation Due to AE Frequentist	Discontinuation Due to AE Bayes1	Discontinuation Due to AE Bayes2
trospium (propiverine)	1.04 (0.72 - 1.51)	1.06 (0.67 - 1.63)	0.99 (0.65 - 1.50)	0.73 (0.44 - 1.22)	0.70 (0.37 - 1.28)	0.67 (0.36 - 1.20)	0.78 (0.45 - 1.36)	0.71 (0.33 - 1.49)	0.90 (0.43 - 1.74)
tolterodine (solifenacin)	**0.77 (0.63 - 0.94)**	0.80 (0.63 - 1.05)	0.81 (0.64 - 1.05)	**0.73 (0.55 - 0.97)**	0.74 (0.50 - 1.08)	0.73 (0.49 - 1.07)	0.77 (0.58 - 1.01)	0.75 (0.53 - 1.09)	0.78 (0.56 - 1.08)
trospium (solifenacin)	1.11 (0.88 - 1.40)	1.16 (0.85 - 1.51)	1.12 (0.87 - 1.48)	0.83 (0.52 - 1.33)	0.80 (0.43 - 1.40)	0.75 (0.41 - 1.29)	0.98 (0.71 - 1.37)	0.95 (0.59 - 1.50)	0.97 (0.65 - 1.43)
trospium (tolterodine)	**1.44 (1.13 - 1.83)**	**1.42 (1.04 - 1.87)**	**1.39 (1.03 - 1.83)**	1.14 (0.75 - 1.72)	1.09 (0.64 - 1.75)	1.04 (0.59 - 1.63)	1.28 (0.95 - 1.74)	1.25 (0.82 - 1.89)	1.25 (0.86 - 1.76)

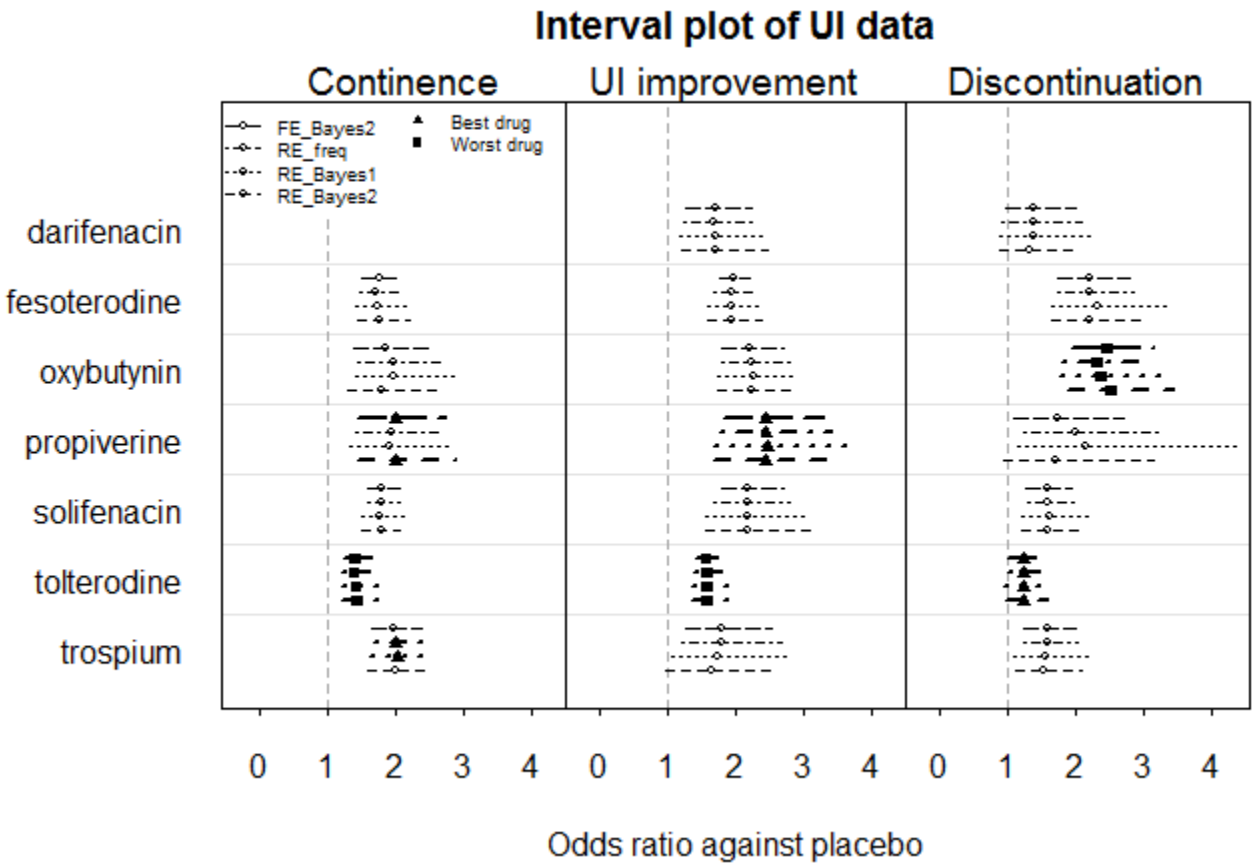
Significant odds ratios are written in bold.

Figure 1. Network graphs of UI data for each outcome



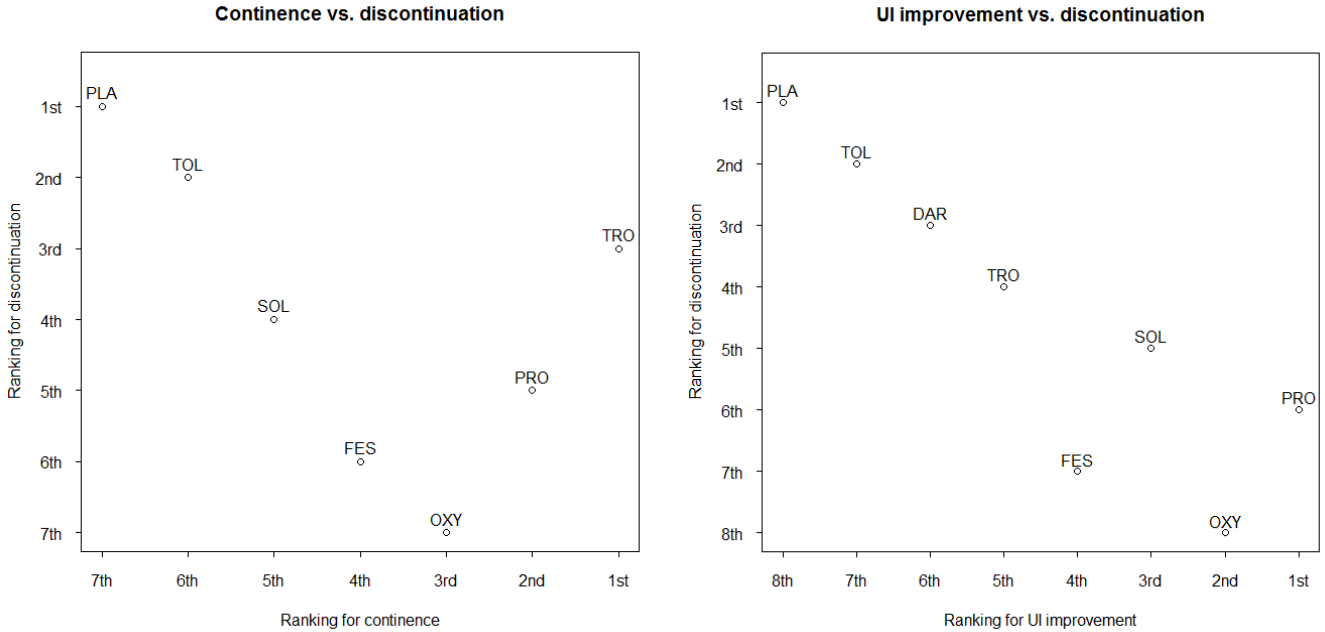
Note: The size of each node represents the number of studies investigating the drug, and the thickness of each edge implies the total number of samples for the relation.

Figure 2. UI data interval plot of odds ratios between drugs and placebo for each outcome



FE_bayes2 = fixed effects model with shrinkage prior; RE_freq = frequentist homogeneous random effects model; RE_Bayes1 = Bayesian homogeneous random effects model with noninformative prior; RE_Bayes2 = Bayesian homogeneous random effects model with shrinkage prior

Figure 3. Ranking of drugs according to two outcomes: (a) continence versus Discontinuation and (b) UI improvement versus discontinuation.



PLA=placebo; DAR=darifenacin; FES=fesoterodine; OXY=oxybutynin; PRO=propiverine; SOL=solifenacin; TOL=tolterodine; TRO=trospium

References

1. Basu A. Economics of individualization in comparative effectiveness research and a basis for a patient-centered health care. J Health Econ. 2011;May;30(3):549-59. Epub April 23, 2011.
2. Committee on Comparative Effectiveness Research Prioritization IoM. Initial National Priorities for Comparative Effectiveness Research. June 30, 2009. www.nap.edu/catalog/12648.html.
3. Institution B. Implementing comparative effectiveness research: Priorities, methods, and impact. The Hamilton Project. 2009 June:1-88.
4. Coory M, Jordan S. Frequency of treatment-effect modification affecting indirect comparisons: a systematic review. Pharmcoeconomics. 2010;28(9):723-32.
5. Wells G, Sultan S, Chen L, et al. Indirect evidence: Indirect treatment comparisons in meta-analysis. Canadian Agency for Drugs and Technologies in Health. 2009;Ottawa.
6. Glenny AM, Altman DG, Song F, et al. Indirect comparisons of competing interventions. Health Technol Assess. 2005 Jul;9(26):1-134, iii-iv. PMID 16014203.
7. Song F, Loke YK, Walsh T, et al. Methodological problems in the use of indirect comparisons for evaluating healthcare interventions: survey of published systematic reviews. BMJ. 2009;338:b1147. PMID 19346285.
8. Donegan S, Williamson P, Gamble C, et al. Indirect comparisons: a review of reporting and methodological quality. PLoS One. 2010;5(11):e11054. PMID 21085712.
9. Jansen JP, Fleurence R, Devine B, et al. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 1. Value Health. 2011 Jun;14(4):417-28. PMID 21669366.
10. Hoaglin DC, Hawkins N, Jansen JP, et al. Conducting indirect-treatment-comparison and network-meta-analysis studies: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 2. Value Health. 2011 Jun;14(4):429-37. PMID 21669367.
11. Dias S, Welton NJ, Caldwell DM, et al. Checking consistency in mixed treatment comparison meta-analysis. Stat Med. 2010 Mar 30;29(7-8):932-44. PMID 20213715.
12. Dias S. WNJ, Sutton A.J.,Caldwell D.M.,Lu C.,Ades A.E.,. Inconsistency in Networks of evidence based on randomized controlled trials. NICE DSU TECHNICAL SUPPORT. 2011;4(May):1-39.
13. Lumley T. Network meta-analysis for indirect treatment comparisons. Stat Med. 2002 Aug 30;21(16):2313-24. PMID 12210616.
14. Shamliyan T, Wyman J, Kane RL. Nonsurgical Treatments for Urinary Incontinence in Adult Women: Diagnosis and Comparative Effectiveness. AHRQ Publication No. 11-EHC074. Rockville, MD. Agency for Healthcare Research and Quality. 2001;36:Prepared by the University of Minnesota Evidence-based Practice Center under Contract No. HHSA 290-2007-10064-I.
15. Haylen BT, de Ridder D, Freeman RM, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. Neurourol Urodyn. 2010;29(1):4-20. PMID 19941278.
16. Abrams P. Incontinence: 4th International Consultation on Incontinence, Paris, July 5-8, 2008: Health Publications Ltd: 2009. Committee 12. Adult Conservative Management.
17. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Devices and Radiological Health, et al. Draft Guidance for Industry and FDA Staff - Clinical Investigations of Devices Indicated for the Treatment of Urinary Incontinence. Rockville, MD 20852: Food and Drug Administration; 2008. www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070852.htm. Accessed August 2009.
18. Coyne KS, Sexton CC, Kopp ZS, et al. The impact of overactive bladder on mental health, work productivity and health-related quality of life in the UK and Sweden: results from EpiLUTS. BJU Int. 2011 Mar 3. PMID 21371240.

19. Berry SM, Ishak KJ, Luce BR, et al. Bayesian meta-analyses for comparative effectiveness and informing coverage decisions. Med Care. 2010 Jun;48(6 Suppl):S137-44. PMID 20473185.

20. O'Regan C, Ghement I, Eyawo O, et al. Incorporating multiple interventions in meta-analysis: an evaluation of the mixed treatment comparison with the adjusted indirect comparison. Trials. 2009;10:86. PMID 19772573.

21. Abrams P. Incontinence: 4th International Consultation on Incontinence, Paris, July 5-8, 2008. 4th ed. [Paris]: Health Publications Ltd.; 2009.

22. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986 Sep;7(3):177-88. PMID 3802833.

23. Smith TC, Speigelhalter DJ, Thomas SL. Bayesian approaches to random-effects meta-analysis: a comparative study. Statistics in Medicine. 1995;14:2685-99.

24. Nixon RM, Bansback N, Brennan A. Using mixed treatment comparisons and meta-regression to perform indirect comparisons to estimate the efficacy of biologic treatments in rheumatoid arthritis. Statistics in Medicine. 2007;26:1237-54.

25. Lu G, Ades A. Assessing evidence inconsistency in Mixed Treatment Comparisons. Journal of the American Statistical Association. 2006;101:447-59.

26. Lu G, Ades A. Combination of direct and indirect evidence in mixed treatment comparisons. Stat Med. 2004 Oct 30;23(20):3105-24. PMID 15449338.

27. Carlin B, Louis T. Bayesian Methods for Data Analysis, 3rd edition. Boca Raton, FL: Chapman and Hall/CRC Press; 2009, page 71.

28. Spiegelhalter D, Best N, Carlin B, et al. Bayesian Measures of Model Complexity and Fit (with Discussion). J Roy Statist Soc, Ser B. 2002;64:583-639.

29. White IR. Multivariate random-effects meta-regression: Updates to mvmeta. The Stata Journal. 2011;11(2)PMID ocn746827598.

30. Jones B, Roger J, Lane PW, et al. Statistical approaches for conducting network meta-analysis in drug development. Pharm Stat. 2011 Nov-Dec;10(6):523-31. PMID 22213533.

31. StataCorp. Stata Statistical Software. Release 12. 2011;College Station, TX (StataCorp LP).

32. Altman DG. Confidence intervals for the number needed to treat. Bmj. 1998 Nov 7;317(7168):1309-12. PMID 9804726.

33. Egger M, Smith GD, Altman DG. Systematic Reviews in Health Care. London: NetLibrary, Inc. BMJ Books; 2001.

34. Ebrahim S. The use of numbers needed to treat derived from systematic reviews and meta-analysis. Caveats and pitfalls. Eval Health Prof. 2001 Jun;24(2):152-64. PMID 11523384.

35. Lunn D, Thomas A, Best N, et al. WinBUGS- a Bayesian modelling framework: concepts, structure, and extensibility. Statistics and Computing. 2000;10:325-37.

36. SAS Institute Inc. C, NC, USA. SAS 9.2. Copyright © 2009. 2012.

37. Cipriani A, Barbui C, Salanti G, et al. Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis. Lancet. 2011 Oct 8;378(9799):1306-15. PMID 21851976.

38. Kaplan SA, Schneider T, Foote J, et al. Superior efficacy of fesoterodine over tolterodine with rapid onset: A prospective, head-to-head, placebo-controlled trial. Neurourology and Urodynamics. 2010;29:905-7.

39. NCT00444925. Clinical Trial to Evaluate the Efficacy and Safety of Fesoterodine in Comparison to Tolterodine for Overactive Bladder (OAB). www.clinicaltrials.gov/ct2/show/NCT00444925?term=NCT00444925&rank=1.

40. Junemann KP, Hessdorfer E, Unamba-Oparah I, et al. Propiverine hydrochloride immediate and extended release: comparison of efficacy and tolerability in patients with overactive bladder. Urol Int. 2006;77(4):334-9. PMID 17135784.

41. Zinner N, Gittelman M, Harris R, et al. Trospium chloride improves overactive bladder symptoms: a multicenter phase III trial. J Urol. 2004 Jun;171(6 Pt 1):2311-5, quiz 435. PMID 15126811.

42. Goode PS. Behavioral and drug therapy for urinary incontinence. Urology. 2004 Mar;63(3 Suppl 1):58-64. PMID 15013654.

43. Moore KH, Hay DM, Imrie AE, et al. Oxybutynin hydrochloride (3 mg) in the treatment of women with idiopathic detrusor instability. Br J Urol. 1990 Nov;66(5):479-85. PMID 2249115.

44. Dorschner W, Stolzenburg JU, Griebenow R, et al. Efficacy and cardiac safety of propiverine in elderly patients - a double-blind, placebo-controlled clinical study. Eur Urol. 2000 Jun;37(6):702-8. PMID 10828671.

45. Vardy MD, Mitcheson HD, Samuels TA, et al. Effects of solifenacin on overactive bladder symptoms, symptom bother and other patient-reported outcomes: results from VIBRANT - a double-blind, placebo-controlled trial. Int J Clin Pract. 2009 Dec;63(12):1702-14. PMID 19930331.

46. Staskin DR, Dmochowski RR, Sand PK, et al. Efficacy and safety of oxybutynin chloride topical gel for overactive bladder: a randomized, double-blind, placebo controlled, multicenter study. J Urol. 2009 Apr;181(4):1764-72. PMID 19233423.

47. Chu F, Smith N, Uchida T. Efficacy and safety of solifenacin succinate 10 mg once Daily: A multicenter, phase III, randomized, double-blind, placebo-controlled, parallel-group trial in patients with overactive bladder. Current Therapeutic Research. 2009 December;70(6):405-20. PMID 10.1016/j.curtheres.2009.11.001.

48. Cardozo L, Castro-Diaz D, Gittelman M, et al. Reductions in overactive bladder-related incontinence from pooled analysis of phase III trials evaluating treatment with solifenacin. Int Urogynecol J Pelvic Floor Dysfunct. 2006 Sep;17(5):512-9. PMID 16625311.

49. Staskin DR, Te AE. Short- and long-term efficacy of solifenacin treatment in patients with symptoms of mixed urinary incontinence. BJU Int. 2006 Jun;97(6):1256-61. PMID 16686722.

50. Karram MM, Toglia MR, Serels SR, et al. Treatment with solifenacin increases warning time and improves symptoms of overactive bladder: results from VENUS, a randomized, double-blind, placebo-controlled trial. Urology. 2009 Jan;73(1):14-8. PMID 18995887.

51. Sand PK, Dmochowski RR, Zinner NR, et al. Trospium chloride extended release is effective and well tolerated in women with overactive bladder syndrome. Int Urogynecol J Pelvic Floor Dysfunct. 2009 Aug 29 PMID 19727537.

52. Staskin D, Sand P, Zinner N, et al. Once daily trospium chloride is effective and well tolerated for the treatment of overactive bladder: results from a multicenter phase III trial. J Urol. 2007 Sep;178(3 Pt 1):978-83; discussion 83-4. PMID 17632131.

53. Herschorn S, Swift S, Guan Z, et al. Comparison of fesoterodine and tolterodine extended release for the treatment of overactive bladder: a head-to-head placebo-controlled trial. BJU Int. 2010 Jan;105(1):58-66. PMID 20132103.

54. Homma Y, Paick JS, Lee JG, et al. Clinical efficacy and tolerability of extended-release tolterodine and immediate-release oxybutynin in Japanese and Korean patients with an overactive bladder: a randomized, placebo-controlled trial. BJU Int. 2003 Nov;92(7):741-7. PMID 14616458.

55. Abrams P, Freeman R, Anderstrom C, et al. Tolterodine, a new antimuscarinic agent: as effective but better tolerated than oxybutynin in patients with an overactive bladder. Br J Urol. 1998 Jun;81(6):801-10. PMID 9666761.

56. Steers W, Corcos J, Foote J, et al. An investigation of dose titration with darifenacin, an M3-selective receptor antagonist. BJU Int. 2005 Mar;95(4):580-6. PMID 15705084.

57. Hill S, Khullar V, Wyndaele JJ, et al. Dose response with darifenacin, a novel once-daily M3 selective receptor antagonist for the treatment of overactive bladder: results of a fixed dose study. Int Urogynecol J Pelvic Floor Dysfunct. 2006 May;17(3):239-47. PMID 15999217.

58. Chapple C, DuBeau C, Ebinger U, et al. Darifenacin treatment of patients >or= 65 years with overactive bladder: results of a randomized, controlled, 12-week trial. Curr Med Res Opin. 2007 Oct;23(10):2347-58. PMID 17706004.

59. Dmochowski RR, Peters KM, Morrow JD, et al. Randomized, double-blind, placebo-controlled trial of flexible-dose fesoterodine in subjects with overactive bladder. Urology. 2010 Jan;75(1):62-8. PMID 19931895.

60. Thuroff JW, Bunke B, Ebner A, et al. Randomized, double-blind, multicenter trial on treatment of frequency, urgency and incontinence related to detrusor hyperactivity: oxybutynin versus propantheline versus placebo. J Urol. 1991 Apr;145(4):813-6; discussion 6-7. PMID 2005707.

61. Herschorn S, Heesakkers J, Castro-Diaz D, et al. Effects of tolterodine extended release on patient perception of bladder condition and overactive bladder symptoms*. Curr Med Res Opin. 2008 Dec;24(12):3513-21. PMID 19032133.

62. Lee JG, Hong JY, Choo MS, et al. Tolterodine: as effective but better tolerated than oxybutynin in Asian patients with symptoms of overactive bladder. Int J Urol. 2002 May;9(5):247-52. PMID 12060436.

63. Lehtoranta K, Tainio H, Lukkari-Lax E, et al. Pharmacokinetics, efficacy, and safety of intravesical formulation of oxybutynin in patients with detrusor overactivity. Scand J Urol Nephrol. 2002 Feb;36(1):18-24. PMID 12002352.

64. Rogers R, Bachmann G, Jumadilova Z, et al. Efficacy of tolterodine on overactive bladder symptoms and sexual and emotional quality of life in sexually active women. Int Urogynecol J Pelvic Floor Dysfunct. 2008 Nov;19(11):1551-7. PMID 18685795.

65. Malone-Lee JG, Al-Buheissi S. Does urodynamic verification of overactive bladder determine treatment success? Results from a randomized placebo-controlled study. BJU Int. 2009 Apr;103(7):931-7. PMID 19281469.

66. Dmochowski RR, Sand PK, Zinner NR, et al. Trospium 60 mg once daily (QD) for overactive bladder syndrome: results from a placebo-controlled interventional study. Urology. 2008 Mar;71(3):449-54. PMID 18342185.

67. Sand PK, Morrow JD, Bavendam T, et al. Efficacy and tolerability of fesoterodine in women with overactive bladder. Int Urogynecol J Pelvic Floor Dysfunct. 2009 Jul;20(7):827-35. PMID 19495545.

68. Madersbacher H, Halaska M, Voigt R, et al. A placebo-controlled, multicentre study comparing the tolerability and efficacy of propiverine and oxybutynin in patients with urgency and urge incontinence. BJU Int. 1999 Oct;84(6):646-51. PMID 10510109.

69. Johnson TM, 2nd, Burgio KL, Redden DT, et al. Effects of behavioral and drug therapy on nocturia in older incontinent women. J Am Geriatr Soc. 2005 May;53(5):846-50. PMID 15877562.

70. Wang AC, Chih SY, Chen MC. Comparison of electric stimulation and oxybutynin chloride in management of overactive bladder with special reference to urinary urgency: a randomized placebo-controlled trial. Urology. 2006 Nov;68(5):999-1004. PMID 17113893.

71. Szonyi G, Collas DM, Ding YY, et al. Oxybutynin with bladder retraining for detrusor instability in elderly people: a randomized controlled trial. Age Ageing. 1995/07/01 ed; 1995. p. 287-91.

72. Lee KS, Lee HW, Choo MS, et al. Urinary urgency outcomes after propiverine treatment for an overactive bladder: the 'Propiverine study on overactive bladder including urgency data'. BJU Int. 2010 Jun;105(11):1565-70. PMID 19912183.

73. Toglia MR, Serels SR, Laramee C, et al. Solifenacin for overactive bladder: patient-reported outcomes from a large placebo-controlled trial. Postgrad Med. 2009 Sep;121(5):151-8. PMID 19820284.

74. Kelleher CJ, Reese PR, Pleil AM, et al. Health-related quality of life of patients receiving extended-release tolterodine for overactive bladder. The American journal of managed care; 2002. p. S608-15.

75. Rogers RG, Bachmann G, Scarpero H, et al. Effects of tolterodine ER on patient-reported outcomes in sexually active women with overactive bladder and urgency urinary incontinence. Curr Med Res Opin. 2009 Sep;25(9):2159-65. PMID 19601704.

76. Staskin DR, Harnett MD. Effect of trospium chloride on somnolence and sleepiness in patients with overactive bladder. Curr Urol Rep. 2004 Dec;5(6):423-6. PMID 15541209.

77. Zinner N, Tuttle J, Marks L. Efficacy and tolerability of darifenacin, a muscarinic M3 selective receptor antagonist (M3 SRA), compared with oxybutynin in the treatment of patients with overactive bladder. World J Urol. 2005 Sep;23(4):248-52. PMID 16096831.

78. Chapple C, Van Kerrebroeck P, Tubaro A, et al. Clinical efficacy, safety, and tolerability of once-daily fesoterodine in subjects with overactive bladder. Eur Urol. 2007 Oct;52(4):1204-12. PMID 17651893.

79. Drutz HP, Appell RA, Gleason D, et al. Clinical efficacy and safety of tolterodine compared to oxybutynin and placebo in patients with overactive bladder. Int Urogynecol J Pelvic Floor Dysfunct. 1999;10(5):283-9. PMID 10543335.

80. Yamaguchi O, Marui E, Kakizaki H, et al. Randomized, double-blind, placebo- and propiverine-controlled trial of the once-daily antimuscarinic agent solifenacin in Japanese patients with overactive bladder. BJU Int. 2007 Sep;100(3):579-87. PMID 17669143.

81. Chapple CR, Rechberger T, Al-Shukri S, et al. Randomized, double-blind placebo- and tolterodine-controlled trial of the once-daily antimuscarinic agent solifenacin in patients with symptomatic overactive bladder. BJU Int. 2004 Feb;93(3):303-10. PMID 14764127.

82. Chapple CR. Darifenacin: a novel M3 muscarinic selective receptor antagonist for the treatment of overactive bladder. Expert Opin Investig Drugs. 2004 Nov;13(11):1493-500. PMID 15500396.

83. Zinner N, Susset J, Gittelman M, et al. Efficacy, tolerability and safety of darifenacin, an M(3) selective receptor antagonist: an investigation of warning time in patients with OAB. Int J Clin Pract. 2006 Jan;60(1):119-26. PMID 16409440.

84. U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Medical Review for Enablex (Clarifenacin) Extended Release Tablets. 2004. www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-513_Enablex.cfm. Accessed on June 25 2010.

85. U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Statistical Review for Enablex (Darifenacin Hydrobromide) Extended Release Tablets. 2004. www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-513_Enablex.cfm. Accessed on June 25 2010.

86. Chapple C. Fesoterodine a new effective and well-tolerated antimuscarinic for the treatment of urgency-frequency syndrome:results of a phase 2 controlled study. 2004 Congress of the International Continence Society; August 25-27, 2004; Paris, France. Abstract 142. 2004.

87. Cardozo L, Hessdorfer E, Milani R, et al. Solifenacin in the treatment of urgency and other symptoms of overactive bladder: results from a randomized, double-blind, placebo-controlled, rising-dose trial. BJU Int. 2008 Nov;102(9):1120-7. PMID 18990175.

88. Rentzhog L, Stanton SL, Cardozo L, et al. Efficacy and safety of tolterodine in patients with detrusor instability: a dose-ranging study. Br J Urol. 1998 Jan;81(1):42-8. PMID 9467475.

89. Malone-Lee JG, Walsh JB, Maugourd MF. Tolterodine: a safe and effective treatment for older patients with overactive bladder. J Am Geriatr Soc. 2001 Jun;49(6):700-5. PMID 11454106.

90. Jacquetin B, Wyndaele J. Tolterodine reduces the number of urge incontinence episodes in patients with an overactive bladder. Eur J Obstet Gynecol Reprod Biol. 2001 Sep;98(1):97-102. PMID 11516807.

91. Khullar V, Hill S, Laval KU, et al. Treatment of urge-predominant mixed urinary incontinence with tolterodine extended release: a randomized, placebo-controlled trial. Urology. 2004 Aug;64(2):269-74; discussion 74-5. PMID 15302476.

92. Rudy D, Cline K, Harris R, et al. Multicenter phase III trial studying trospium chloride in patients with overactive bladder. Urology. 2006 Feb;67(2):275-80. PMID 16461077.

93. U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Medical Review for Sanctura XR (Trospium Chloride) Extended Release Capsules. 2007. www.accessdata.fda.gov/drugsatfda_docs/nda/2007/022103s000TOC.cfm. Accessed on June 25 2010.

94. U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Statistical Review for Sanctura XR (Trospium Chloride) Extended Release Capsules. 2007. www.accessdata.fda.gov/drugsatfda_docs/nda/2007/022103s000TOC.cfm. Accessed on June 25 2010.

95. Chapple CR, Abrams P. Comparison of darifenacin and oxybutynin in patients with overactive bladder: assessment of ambulatory urodynamics and impact on salivary flow. Eur Urol. 2005 Jul;48(1):102-9. PMID 15936869

96. Appell RA, Sand P, Dmochowski R, et al. Prospective randomized controlled trial of extended-release oxybutynin chloride and tolterodine tartrate in the treatment of overactive bladder: results of the OBJECT Study. Mayo Clin Proc. 2001 Apr;76(4):358-63. PMID 11322350.

97. Armstrong RB, Luber KM, Peters KM. Comparison of dry mouth in women treated with extended-release formulations of oxybutynin or tolterodine for overactive bladder. Int Urol Nephrol. 2005;37(2):247-52. PMID 16142551.

98. Appell RA. Clinical efficacy and safety of tolterodine in the treatment of overactive bladder: a pooled analysis. Urology. 1997 Dec;50(6A Suppl):90-6; discussion 7-9. PMID 9426760.

99. Zellner M, Madersbacher H, Palmtag H, et al. Trospium chloride and oxybutynin hydrochloride in a german study of adults with urinary urge incontinence: results of a 12-week, multicenter, randomized, double-blind, parallel-group, flexible-dose noninferiority trial. Clin Ther. 2009 Nov;31(11):2519-39. PMID 20109997.

100. Halaska M, Ralph G, Wiedemann A, et al. Controlled, double-blind, multicentre clinical trial to investigate long-term tolerability and efficacy of trospium chloride in patients with detrusor instability. World J Urol. 2003 May;20(6):392-9. PMID 12811500.

101. Pharmaceutical Research and Manufacturers of America. Solifenacin in a flexible dose regimen with tolterodine as an active comparator in a double-blind, double-dummy, randomized overactive bladder symptom trial (STAR). www.clinicalstudyresults.org/documents/company-study_8350_0.pdf. Accessed on June 25 2010.

102. Choo MS, Lee JZ, Lee JB, et al. Efficacy and safety of solifenacin succinate in Korean patients with overactive bladder: a randomised, prospective, double-blind, multicentre study. Int J Clin Pract. 2008 Nov;62(11):1675-83. PMID 19143854.

Abbreviations

AE	Adverse effect
AIC	Akaike information criterion
ARD	Absolute risk difference
DIC	Deviance information criterion
FDA	Food and Drug Administration
MCMC	Markov chain Monte Carlo
MTC	Mixed (or multiple) treatment comparison
NNT	Number needed to treat
OAB	Overactive bladder
RCT	Randomized controlled trial
UI	Urinary incontinence

Appendix A. Summary of Bayesian Models Under the Noninformative Prior

Fixed effect model	Random effect model (homogeneous)	Random effect model (heterogeneous)	Random effect model (inconsistency)
Data $r_{ik} \sim Bin(n_{ik}, p_{ik})$ i = 1, …, NS; k = 1, …, NT (NS = number of study; NT = number of trt) **Model** $logit(p_{ik}) = \mu_{iB} + \Delta_{Bk}$ where B is for the baseline treatment, μ_{iB} is the log odds of the baseline treatment and Δ_{Bk} is the fixed effect of the k^{th} drug versus the baseline treatment defined by $d_k - d_B$ with the fixed effect of the k^{th} drug versus placebo, d_k ($d_B = 0$) **Prior** $d_k \sim N(0, 10000)$ $\mu_{iB} \sim N(0, 10000)$	**Data** $r_{ik} \sim Bin(n_{ik}, p_{ik})$ **Model** $logit(p_{ik}) = \mu_{iB} + \delta_{iBk}$ where δ_{iBk} is the random effect of the k^{th} drug versus the baseline treatment in the i^{th} study **Prior** $\delta_{iBk} \sim N(d_k - d_B, \sigma^2)$ $d_k \sim N(0, 10000)$ $\mu_{iB} \sim N(0, 10000)$ $\sigma \sim Unif(0.01,2)$	**Data** $r_{ik} \sim Bin(n_{ik}, p_{ik})$ **Model** $logit(p_{ik}) = \mu_{iB} + \delta_{iBk}$ where δ_{iBk} is the random effect of the k^{th} drug versus the baseline treatment in the i^{th} study **Prior** $\delta_{iBk} \sim N(d_k - d_B, \sigma_{Bk}^2)$ $d_k \sim N(0, 10000)$ $\mu_{iB} \sim N(0, 10000)$ $log\sigma_{xy} = log\sigma_0 + v_{xy}$ $\sigma_0 \sim Unif(0.01,2)$ $v_{xy} \sim N(0, \psi^2)$	**Data** $r_{ik} \sim Bin(n_{ik}, p_{ik})$ **Model** $logit(p_{ik}) = \mu_{iB} + \delta_{iBk}$ where δ_{ik} is the random effect of of the k^{th} drug versus the placebo in the i^{th} study 1. $d_{BC} = d_{AC} - d_{AB} + w_{ABC}$ w_{ABC} is the amount of inconsistency between direct and indirect comparisons **Prior** $\delta_{iBk} \sim N(d_k - d_B, \sigma^2)$ $d_k \sim N(0, 10000)$ $\mu_{iB} \sim N(0, 10000)$ $w_{ABC} \sim N(0, \sigma_w^2)$ $\sigma, \sigma_w \sim Unif(0.01,2)$
[Example] Study 1: Drugs 1 vs. 2 vs. 3 trial (drug 1 is the baseline treatment)			
Fixed effect model	**Random effect model (homogeneous)**	**Random effect model (heterogeneous)**	**Random effect model (inconsistency)**
Data $r_{11} \sim Bin(n_{11}, p_{11})$ $r_{12} \sim Bin(n_{12}, p_{12})$ $r_{13} \sim Bin(n_{13}, p_{13})$ **Model** 2. $logit(p_{11}) = \mu_{11}$ 3. $logit(p_{12}) = \mu_{11} + d_2$ 4. $logit(p_{13}) = \mu_{11} + d_3$ **Prior** $d_2, d_3 \sim N(0, 10000)$ $\mu_{11} \sim N(0, 10000)$	**Model** 5. $logit(p_{11}) = \mu_{11}$ 6. $logit(p_{12}) = \mu_{11} + \delta_{12}$ 7. $logit(p_{13}) = \mu_{11} + \delta_{13}$ **Prior (assume ρ=0.5)** $\begin{pmatrix}\delta_{12}\\ \delta_{13}\end{pmatrix} \sim MVN(\begin{pmatrix}d_2\\ d_3\end{pmatrix}, \sigma^2 \begin{pmatrix}1 & 0.5\\ 0.5 & 1\end{pmatrix})$ ➔ $\delta_{12} \sim N(d_2, \sigma^2)$ ➔ $\delta_{13} \mid \delta_{12} \sim N(d_3 + \frac{1}{2}(\delta_{12} - d_2), \frac{3}{4}\sigma^2)$ $d_2, d_3 \sim N(0, 10000)$ $\mu_{11} \sim N(0, 10000)$ $\sigma \sim Unif(0.01,2)$	**Model** 8. $logit(p_{11}) = \mu_{11}$ 9. $logit(p_{12}) = \mu_{11} + \delta_{12}$ 10. $logit(p_{13}) = \mu_{11} + \delta_{13}$ **Prior (assume ρ=0.5)** $\begin{pmatrix}\delta_{12}\\ \delta_{13}\end{pmatrix} \sim MVN(\begin{pmatrix}d_2\\ d_3\end{pmatrix}, \begin{pmatrix}\sigma_{11}^2 & 0.5\sigma_{12}\\ 0.5\sigma_{12} & \sigma_{22}^2\end{pmatrix})$ ➔ $\delta_{12} \sim N(d_2, \sigma_1^2)$ ➔ $\delta_{13} \mid \delta_{12} \sim N(d_3 + \frac{1}{2}(\delta_{12} - d_2), \frac{3}{4}\sigma_2^2)$ $d_2, d_3 \sim N(0, 10000)$ $\mu_{11} \sim N(0, 10000)$ $log\sigma_{11} = log\sigma_0 + v_{11}$ $log\sigma_{12} = log\sigma_0 + v_{12}$ $log\sigma_{22} = log\sigma_0 + v_{22}$ $\sigma_0 \sim Unif(0.01,2)$ $v_{11}, v_{12}, v_{22} \sim Unif(0.01, \psi^2)$	Study 1: 1 vs. 2 vs. 3 trial 11. Study 2: 1 vs. 2 12. Study 3: 1 vs. 3 ➔ We can estimate w_{123} because the data permit estimation via the equation $d_{23} = d_{13} - d_{13} + w_{123}$ Model and priors are similarly defined as in Model2. Additional prior is $w_{123} \sim N(0, \sigma_w^2)$ $\sigma_w \sim Unif(0.01,2)$

Appendix B. Bugs and SAS Codes for Bayesian and Frequentist Analysis

#BUGS code for fixed effects model under the noninformative prior
#with respect to the UI improvement outcome

```
model {

  for(i in 1:N) {
    logit(p[i]) <- mu[s[i]] + d[t[i]] - d[b[i]]
    r[i] ~ dbin(p[i], n[i])
  }

  for(j in 1:NS) { mu[j] ~ dnorm(0, 0.0001) }

  d[1] <- 0
  for (k in 2:NT) {
    d[k] ~ dnorm(0, 0.0001)
    ed[k] <- exp(d[k])        # ed is odds ratio against placebo
  }

  # pairwise ORs
  # Example: or[2,3] = odds ratio of active(2) vs. control(3)
  for (k in 1:NT) {
    for (c in 1:NT) {
      lor[k,c] <- d[k] - d[c]
      log(or[k,c]) <- lor[k,c]
    }
  }

  # ranking
  mP <- mean(mu[1:27])        # Take average of mu[]

  for (k in 1:NT) { logit(T[k]) <- mP + d[k] }
  for (k in 1:NT) {
    rk[k] <- NT + 1 - rank(T[],k)
    best1[k] <- equals(rk[k],1)
    best2[k] <- equals(rk[k],2)
    best12[k] <- best1[k] + best2[k]
  }
}

#Init
list(
d=c(NA,0,0,0,0,0,0,0),
mu=c(0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0, 0,0,0,0,0, 0,0,0)
)

#Data
#Numbers for drugs:
#1=placebo; 2=darifenacin; 3=fesoterodine; 4=oxybutynin;
#5=propiverine; 6=solifenacin; 7=tolterodine; 8=trospium
list(N=62, NS=28, NT=8)
```

s[]	t[]	r[]	n[]	b[]
1	1	113	334	1
1	3	293	679	1
1	7	256	684	1
2	1	32	337	1
2	3	102	685	1
2	7	79	690	1
3	1	167	430	1
3	3	291	452	1
3	7	140	227	1
4	1	287	480	1
4	3	709	963	1
4	7	654	974	1
5	1	27	57	1
5	4	58	118	1
5	7	59	118	1
6	1	31	122	1
6	4	129	244	1
6	7	100	239	1
7	1	60	127	1
7	2	160	268	1
8	1	15	109	1
8	2	28	108	1
9	1	47	133	1
9	2	122	266	1
10	1	137	445	1
10	3	182	438	1
11	1	15	52	1
11	4	26	63	1
12	1	1	25	1
12	4	10	28	1
13	1	16	29	1
13	4	22	28	1
14	1	20	65	1
14	4	37	67	1
15	1	43	72	1
15	4	116	145	1
16	1	1	38	1
16	4	4	46	1
17	1	0	21	1
17	4	2	23	1
18	1	11	49	1
18	5	19	49	1
19	1	94	202	1
19	5	264	391	1
20	1	12	88	1
20	5	55	176	1
21	1	109	382	1
21	6	196	386	1
22	1	206	367	1
22	6	260	372	1
23	1	218	508	1
23	7	294	507	1
24	1	64	207	1
24	7	156	410	1

```
25      1       58      211     1
25      7       79      202     1
26      1       141     261     1
26      8       186     262     1
27      1       8       326     1
27      8       5       327     1
28      4       53      116     4
28      7       50      112     4
END
```

#BUGS code for homogeneous random effects model under the noninformative prior
#with respect to the UI improvement outcome

```
model {
for (i in 1:NS) {
s[i,1] <- 0
delta[i, t[i,1]] <- 0
mu[i] ~ dnorm(0, 0.0001)

for (k in 1:na[i]) {
     r[i,k] ~ dbin(p[i,t[i,k]], n[i,k])
     logit(p[i,t[i,k]]) <- mu[i] + delta[i,t[i,k]]
   }

for (k in 2:na[i]) {
     delta[i,t[i,k]] ~ dnorm(md[i,t[i,k]], taud[i,t[i,k]])
     md[i,t[i,k]] <- d[t[i,k]] - d[t[i,1]] + ss[i,k]
taud[i,t[i,k]] <- tau*2*(k-1)/k
     s[i,k] <- (delta[i, t[i,k]] - d[t[i,k]] + d[t[i,1]])
ss[i,k] <- sum(s[i, 1:k-1])/(k-1)
   }
 }

d[1] <- 0
for (k in 2:NT) {
d[k] ~ dnorm(0,0.0001)
ed[k] <- exp(d[k])        # ed is odds ratio against placebo
 }

sd~dunif(0.01,2)
tau<- 1/pow(sd,2)
var<- pow(sd,2)

 # pairwise ORs
 # Example: or[2,3] = odds ratio of active(2) vs. control(3)
for (k in 1:NT) {
for (c in 1:NT) {
lor[k,c] <- d[k] - d[c]
log(or[k,c]) <- lor[k,c]
   }
 }

 # ranking
mP<- mean(mu[1:27])        # Take average of mu[]

for (k in 1:NT) { logit(T[k]) <- mP + d[k] }     # T=prob of each trt
```

```
for (k in 1:NT) {
rk[k] <- NT + 1 - rank(T[],k)
best1[k] <- equals(rk[k],1)
best2[k] <- equals(rk[k],2)
best12[k] <- best1[k] + best2[k]
  }
}

#Init
list(
d=c(NA,0,0,0,0,0,0,0),
sd=1,
mu=c(0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0, 0,0,0,0,0,  0,0,0)
)

#Data
list(NT=8, NS=28)
```

r[,1]	n[,1]	r[,2]	n[,2]	r[,3]	n[,3]	t[,1]	t[,2]	t[,3]	na[]
113	334	293	679	256	684	1	3	7	3
32	337	102	685	79	690	1	3	7	3
167	430	291	452	140	227	1	3	7	3
287	480	709	963	654	974	1	3	7	3
27	57	58	118	59	118	1	4	7	3
31	122	129	244	100	239	1	4	7	3
60	127	160	268	NA	1	1	2	NA	2
15	109	28	108	NA	1	1	2	NA	2
47	133	122	266	NA	1	1	2	NA	2
137	445	182	438	NA	1	1	3	NA	2
15	52	26	63	NA	1	1	4	NA	2
1	25	10	28	NA	1	1	4	NA	2
16	29	22	28	NA	1	1	4	NA	2
20	65	37	67	NA	1	1	4	NA	2
43	72	116	145	NA	1	1	4	NA	2
1	38	4	46	NA	1	1	4	NA	2
0	21	2	23	NA	1	1	4	NA	2
11	49	19	49	NA	1	1	5	NA	2
94	202	264	391	NA	1	1	5	NA	2
12	88	55	176	NA	1	1	5	NA	2
109	382	196	386	NA	1	1	6	NA	2
206	367	260	372	NA	1	1	6	NA	2
218	508	294	507	NA	1	1	7	NA	2
64	207	156	410	NA	1	1	7	NA	2
58	211	79	202	NA	1	1	7	NA	2
141	261	186	262	NA	1	1	8	NA	2
8	326	5	327	NA	1	1	8	NA	2
53	116	50	112	NA	1	4	7	NA	2

```
END
```

#BUGS code for heterogeneous random effects model under the noninformative prior
#with respect to the UI improvement outcome

```
model {
  for (i in 1:NS) {
    s[i,1] <- 0
```

```
    delta[i, t[i,1]] <- 0
    mu[i] ~ dnorm(0, 0.0001)

    for (k in 1:na[i]) {
      r[i,k] ~ dbin(p[i,t[i,k]], n[i,k])
      logit(p[i,t[i,k]]) <- mu[i] + delta[i,t[i,k]]
    }

    for (k in 2:na[i]) {
      delta[i,t[i,k]] ~ dnorm(md[i,t[i,k]], taud[i,t[i,k]])
      md[i,t[i,k]] <- d[t[i,k]] - d[t[i,1]] + ss[i,k]
      taud[i,t[i,k]] <- tau[t[i,1],t[i,k]]*2*(k-1)/k
      s[i,k] <- (delta[i, t[i,k]] - d[t[i,k]] + d[t[i,1]])
      ss[i,k] <- sum(s[i, 1:k-1])/(k-1)
    }
  }

  d[1] <- 0
  for (k in 2:NT) {
    d[k] ~ dnorm(0,0.0001)
    ed[k] <- exp(d[k])        # ed is odds ratio against placebo
  }

  for(i in 1:(NT-1)) {
    for(j in (i+1):NT) {
      v[i,j] ~ dnorm(0, 8.32)
      log(sd[i,j]) <- log(sd0) + v[i,j]
      tau[i,j] <- 1/pow(sd[i,j],2)
      var[i,j] <- pow(sd[i,j],2)
    }
  }
  sd0 ~ dunif(0.01,2)
  var0 <- pow(sd0,2)

  # pairwise ORs
  # Example: or[2,3] = odds ratio of active(2) vs. control(3)
  for (k in 1:NT) {
    for (c in 1:NT) {
      lor[k,c] <- d[k] - d[c]
      log(or[k,c]) <- lor[k,c]
    }
  }

  # ranking
  mP <- mean(mu[1:27])        # Take average of mu[]

  for (k in 1:NT) { logit(T[k]) <- mP + d[k] }
  for (k in 1:NT) {
    rk[k] <- NT + 1 - rank(T[],k)
    best1[k] <- equals(rk[k],1)
    best2[k] <- equals(rk[k],2)
    best12[k] <- best1[k] + best2[k]
  }
}

#Init
```

```
list(
d=c(NA,0,0,0,0,0,0,0),
sd0=1,
mu=c(0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0, 0,0,0,0,0,  0,0,0)
)

#Data are the same as in Model 2
```

#BUGS code for inconsistency random effects model under the noninformative prior
#with respect to the UI improvement outcome

```
model {
  for (i in 1:NS) {
    s[i,1] <- 0
    delta[i, t[i,1]] <- 0
    mu[i] ~ dnorm(0, 0.0001)

    for (k in 1:na[i]) {
      r[i,k] ~ dbin(p[i,t[i,k]], n[i,k])
      logit(p[i,t[i,k]]) <- mu[i] + delta[i,t[i,k]]
    }

    for (k in 2:na[i]) {
      delta[i,t[i,k]] ~ dnorm(md[i,t[i,k]], taud[i,t[i,k]])
      md[i,t[i,k]] <- dd[t[i,k],t[i,1]] + ss[i,k]
      taud[i,t[i,k]] <- tau*2*(k-1)/k
      s[i,k] <- (delta[i, t[i,k]] - dd[t[i,k],t[i,1]])
      ss[i,k] <- sum(s[i, 1:k-1])/(k-1)
    }
  }

  dd[7,3] <- d[7] - d[3] + wf[1]
  dd[7,4] <- d[7] - d[4] + wf[2]
  or73 <- exp(dd[7,3])
  or74 <- exp(dd[7,4])

  d[1] <- 0
  for (k in 2:NT) {
    dd[k,1] <- d[k]
    d[k] ~ dnorm(0, 0.0001)
    ed[k] <- exp(d[k])        # ed is odds ratio against placebo
  }
  for (i in 1:2) {
    wf[i] ~ dnorm(0, tau.w)
  }

  sd~dunif(0.01,2)
  tau <- 1/pow(sd,2)
  var <- pow(sd,2)

  sd.w ~ dunif(0.01,2)
  var.w <- pow(sd.w, 2)
  tau.w <- 1/var.w

  IP <- step(var.w-var)
```

```
  # pairwise ORs
  # Example: or[2,3] = odds ratio of active(2) vs. control(3)
  for (k in 1:NT) {
    for (c in 1:NT) {
      lor[k,c] <- d[k] - d[c]
      log(or[k,c]) <- lor[k,c]
    }
  }

  # ranking
  mP <- mean(mu[1:27])        # Take average of mu[]

  for (k in 1:NT) { logit(T[k]) <- mP + d[k] }
  for (k in 1:NT) {
    rk[k] <- NT + 1 - rank(T[],k)
    best1[k] <- equals(rk[k],1)
    best2[k] <- equals(rk[k],2)
    best12[k] <- best1[k] + best2[k]
  }
}

#Init
list(
d=c(NA,0,0,0,0,0,0,0),
sd=1,
sd.w=1,
mu=c(0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0, 0,0,0,0,0,  0,0,0)
)

#Data are the same as in Model 2
```

#SAS code for frequntist analysis with respect to the UI improvement outcome

```
/* Numbering of drugs are different from in the WinBUGS code */
/* since SAS consider the largest number as reference group */
/* 1=trospium; 2=tolterodine; 3=solifenacin; 4=propiverine; */
/* 5=oxybutynin; 6=fesoterodine; 7=darifenacin; 8=placebo */

data UI_imp;
input Study trt r n Narm Index Revindex Notfirst NotLast;
datalines;
1       2       256     684     3       1       3       0       1
1       6       293     679     3       2       2       1       1
1       8       113     334     3       3       1       1       0
2       2       79      690     3       1       3       0       1
2       6       102     685     3       2       2       1       1
2       8       32      337     3       3       1       1       0
...
;
run;

/* Fixed effects model */
proc genmod data=UI_imp;
class study trt;
model R/N = Study trt /link=logit dist=bin ;
lsmeans trt /diff  cl;
run;
```

```
/* Random effects model */
data UI_imp2;
set UI_imp;
array x[3] x1-x3;
do i=1 to 3;
        if i<= narm then x[i]=sqrt(0.5)*((i=index)-1/narm);
        else x[i]=0;
end;
run;

proc glimmix data=UI_imp2 method=QUAD;
class study Trt  ;
model R/N = Trt Study/link=logit dist=bin ddfm=none;
random X1 X2 X3/ subject=study type=TOEP(1) ;
lsmeans Trt /diff cl oddsratios;
run;
```

Appendix C. Randomized Controlled Clinical Trials That Examined Drugs for Urgency Urinary Incontinence

Reference Study, Sample	Inclusion Criteria	Exclusion Criteria	Active	Control	Sponsorship
Abrams, 1998[1] Study: RCT Sample: 293	Men and women aged ≥18 years having urodynamically confirmed bladder overactivity, an increased frequency of micturition (≥8 micturitions/24h) and urge incontinence (≥1 incontinent episode/24h) and /or urgency during a 2-week washout/run-in period	Clinically significant stress incontinence; detrusor hyper-reflexia; hepatic, renal or hematological disorders; symptomatic or recurrent urinary tract infection; bladder outlet obstruction; those receiving bladder training, electro stimulation therapy; those with an indwelling catheter or who were on intermittent catheterization; pregnant or nursing women; or women of childbearing age who were not using reliable contraception	Tolterodine	Oxybutynin	Pharmacia and Upjohn AB, Uppsala. Sweden
Appell, 1997[2] Pooled Country: not reported N: 1120	Pooled analysis of 4 RCTS: men and women with detrusor overactivity (phasic detrusor contraction with an amplitude 2 10 cm H,O); and 4) urinary frequency (an average of 28 micturitions/24 hours) and urge incontinence (an average of ≥1 incontinence episode/24 hours) or urinary frequency.	Clinically significant stress incontinence; hepatic or renal disease; recurrent urinary tract infections (UTIs); interstitial cystitis; uninvestigated hematuria or hematuria secondary to malignant disease; indwelling catheter or intermittent catheterization; treatment with any investigational drug in the 2 months prior to entry; previous treatment with Tolterodine; electro stimulation therapy or bladder training within 14 days prior to entry or initiation during the study; treatment with any anti-cholinergic drug or any drug for urinary incontinence within 14 days prior to the baseline visit or initiation during the study; unstable dosage of any treatment with	Tolterodine 2 mg twice daily; tolterodine 1 mg twice daily; oxybutynin (5 mg three times daily)	Placebo	Not reported

Reference Study, Sample	Inclusion Criteria	Exclusion Criteria	Active	Control	Sponsorship
		anticholinergic side effects of initiation of such treatment during the study; previously demonstrated serious side effects on oxybutynin; an average total voided volume >3,000ml/24 hours; and clinically significant voiding difficulty with risk of urinary retention.			
Appell, 2001[3,4] The OBJECT (Overactive Bladder: Judging Effective Control and Treatment) US N: 378	Participants with overactive bladder who had between 7 and 50 episodes of urge incontinence per week and 10 or more voids per 24 hours were included. Those with mixed stress and urge incontinence were eligible if the majority of the leakage accidents were related to urge incontinence.	Urinary tract infection, prostatitis, interstitial cystitis, urinary tract obstruction, urethral diverticulum, bladder tumor, bladder stone, prostate cancer were excluded, as were those who had delivered a baby or undergone pelvic, vaginal, bladder, or prostate surgery less than 6 months before study enrollment; participants with a post-void residual urine volume of more than 150ml at the time of screening; those at considerable risk of developing complete urinary retention if placed on an anti-muscarinic agent; those with clinically important medical problems or other organ abnormalities or pathologies for whom administration of extended-release oxybutynin or Tolterodine would present undue risk (medically uncontrolled cardiovascular, pulmonary, gastrointestinal, renal, endocrine, neurological, autoimmune, hematological, urological, or psychiatric disorders; severely reduced	10 mg/d of extended-release oxybutynin chloride	2 mg twice daily of tolterodine tartrate	AlZA Corporation, Mountain View, California

Reference Study, Sample	Inclusion Criteria	Exclusion Criteria	Active	Control	Sponsorship
		hepatic function or renal impairment); subjects with hematuria, or a positive urine culture; those with narrow-angle glaucoma; obstructive uropathy; myasthenia gravis; pelvic organ prolapse to the hymenal ring; gastrointestinal conditions such as partial or complete obstruction, preexisting severe gastrointestinal narrowing (pathologic or iatrogenic), decreased gastrointestinal motility (paralytic ileus, intestinal atony, chronic and severe constipation), or risk of gastric retention; those who had taken an investigational drug within the previous month; those with known allergies or hypersensitivities to oxybutynin chloride, tolterodine tartrate, or components of the respective drugs; current alcohol or other drug abuse; women who were pregnant or breastfeeding; those who were not capable of following the study schedule or directions; and those who were not able to swallow the medication without chewing, crushing, biting, dividing, or dissolving the capsule			
Burgio, 1998[5-7] RCT USA N: 197	Adults with at least 2 urge accidents per week on the 2-week baseline bladder diary, and urge incontinence had to be the predominant	Continual leakage, post void residual urine volume >200 mL, uterine prolapse past the introitus, narrow-angle glaucoma, unstable angina, decompensated congestive heart failure, history of	Oxybutynin chloride, possible range of doses, 2.5 mg daily to 5.0 mg 3 times daily	Behavioral Training: biofeedback-assisted PFMT/ placebo	Grants AG08010

Reference Study, Sample	Inclusion Criteria	Exclusion Criteria	Active	Control	Sponsorship
	pattern (the number of urge accidents had to exceed the number of stress accidents). Also, there had to be urodynamic evidence of bladder dysfunction (detrusor instability filling or provocation or maximal cystometric capacity of ≤350ml).	malignant arrhythmias, or impaired mental status (MMSE score <20).			
Cardozo, 2006[8] Pooled NR N: 3,298	Men and women at least 18 years of age with a mean of >8 micturitions/day; >1 incontinence episode/day; >1 urgency episode/day	Reported previously	Solifenacin 5 mg; solifenacin 10mg	Placebo	Grant from Yamanouchi Pharmaceutical Co., Ltd., Tokyo, Japan.
Chapple, 2007[9,10] RCT Belgium, Bulgaria, Czech Republic, Estonia, France, Germany, Hungary, Italy, the Netherlands, Poland, Romania, Russia, Spain, Sweden, Ukraine, the United Kingdom, South Africa, Australia, and New Zealand N: 1,135	Men and women with OAB symptoms with urinary urgency for >6 months and >3 UUI episodes per 24 hours (symptoms were recorded in a 3-day diary).	Pregnancy ;non adequate contraception throughout the trial; lower urinary tract pathology that could, in the investigator's opinion, be responsible for urgency or incontinence (e.g., genuine stress incontinence, bladder stones, interstitial cystitis urothelial tumours), pelvic prolapse of grade III or higher, clinically relevant bladder outlet obstruction, polyuria (>3 l per 24 hours), symptomatic or recurrent urinary tract infections, or post void residual (PVR) urine volume >100 ml; currently receiving treatment, were treated within 2 weeks of screening visit with antimuscarinic agents, were treated within the past 4	Tolterodine ER 4 mg, fesoterodine 4 mg, fesoterodine 8 mg	Placebo	Schwarz BioSciences GmbH and Pfizer Inc

Reference Study, Sample	Inclusion Criteria	Exclusion Criteria	Active	Control	Sponsorship
		weeks with electro stimulation for bladder training, or had an active urinary tract infection or an underlying neurological disease responsible for their OAB; cardiac arrhythmia and/or unstable angina or a QTcB interval >500 ms.			
Chapple, 2007[11] RCT USA, Poland, South Africa, Hungary, Sweden, UK and Germany N: 400	Men and women >65 years of age with OAB for at least 6 month with >1 urge UI/day and >10 micturitions/day	Dependent toileting, dependent diary completion, taking drugs that can affect bladder function or external urethral sphincter, total daily volume >3000ml, mean volume/micturition >300ml, clinically significant stress UI or bladder outlet obstruction (post void residual volume >100ml); marked cystocele, stage 3 or 4 pelvic prolapse; participation in bladder training program or electrical stimulation therapy within 3 months of screening; intermittent urinary tract infection, clinically significant congenital or acquired disorder of the urinary tract, chronic pain syndrome or other clinically significant medical conditions including cognitive impairment, uncontrolled severe hypertension, uncontrolled severe heart failure, recent myocardial infarction, or uncontrolled thyroid disease.	Darifenacin (7.5 mg once daily for 2 weeks, then optional titration to 15 mg daily)	Placebo	Not reported
Chapple, 2005[12] RCT USA N: 65	Men and women aged 18–75 years with cystometric evidence of detrusor	Previous bladder surgery for detrusor overactivity; prostatectomy in the last 6 months; bladder stones;	Darifenacin immediate release (IR) 2.5 mg three times a day (t.i.d.); darifenacin	Oxybutynin 2.5 mg t.i.d.; oxybutynin 5 mg t.i.d.; oxybutynin 5 mg t.i.d.	Pfizer Inc

Reference Study, Sample	Inclusion Criteria	Exclusion Criteria	Active	Control	Sponsorship
	overactivity within the previous 6 months, either idiopathic or neurogenic (secondary to a neurological lesion present for >12 months), with >2 associated symptoms (average of >7 micturitions/day, >7 episodes of urgency/week, >1 urge incontinence episode/week necessitating change of clothing or pads).	treatment with diuretics, antimuscarinic, tricyclic antidepressants or digoxin within the previous 2 weeks; stress and mixed incontinence, unless detrusor overactivity was the principal urodynamic observation and the patient was experiencing normal recommended limits, contraindications to anticholinergics (e.g. untreated or narrow angle glaucoma, bladder outlet obstruction).	controlled release (CR) 15 mg once daily (q.d.); darifenacin CR 30 mg q.d.		
Chapple, 2005[13] Pooled Country: not reported N: 1,059	Men and women aged ≥18 years with symptoms of OAB for ≥6 months, and capable of independent toileting, with 5–50 episodes of incontinence per week during the run-in period, and a high voiding frequency (a mean of ≥8 voids/24 hours) and urgency (a mean of ≥1 episode/24 hours); women of childbearing potential required to use an adequate method of contraception throughout the study; those taking hormone–replacement therapy had to have received	Initiation of a bladder training; pregnancy and lactation; clinically significant stress incontinence (i.e.>1 episode of stress incontinence per week), BOO and/or a post void residual urine volume of > 200 mL (as measured by pelvic ultrasonography); clinically important medical problems that would interfere with the patient's participation in the study; patients with interstitial cystitis, severe constipation (two or fewer bowel movements per week), hematuria or intermittent UTI; cystocele or other clinically significant pelvic prolapsed; patients with an indwelling catheter and those who practiced intermittent self-catheterization; urogenital surgery in the previous 6	Darifenacin 7.5 mg or 15 mg/day	Placebo	The studies were funded by Pfizer Inc.

Reference Study, Sample	Inclusion Criteria	Exclusion Criteria	Active	Control	Sponsorship
	such therapy for ≥2 months before entering the study; men taking finasteride for BPH had to be on a stable dose for ≥2 months; those receiving long-term therapy with diuretics, antihypertensive medications, benzodiazepines or antihistamines had to be taking a stable dose before study recruitment, with no plans to change treatment during the study; and patients on bladder training program were not to modify or discontinue their training during the course of the study.	months; patients with contraindications to antimuscarinic therapy (e.g., uncontrolled narrow-angle glaucoma, urinary retention, gastric retention); history of alcohol/drug abuse; and known hypersensitivity to study medication.			
Chapple, 2004[14] Study: RCT Sample: 728	Not reported	Not reported	Fesoterodine	Placebo	Not reported
Chapple, 2004[15] Study: RCT Sample: 1081	Men and women aged>=18 years with symptomatic OAB (including urgency, urge incontinence, or frequency) for >=3 months. After run-in period patients had to have had an average frequency of >=8 voids/24 hours and have experienced at least 3 episodes of urgency and/or three	Significant BOO, a post void residual volume of >200mL, incontinence for which stress was determined to be the predominant factor, presence of a neurological cause for detrusor muscle overactivity, evidence of UTI or bladder stones, previous pelvic irradiation, or previous or current malignant disease of the pelvic organs, any medical condition contraindicating the use of	Solifenacin 5mg and 10mg	Tolterodine 2mg twice daily or placebo	Yamanouchi Pharma Co., Ltd, Tokyo,Japan

Reference Study, Sample	Inclusion Criteria	Exclusion Criteria	Active	Control	Sponsorship
	episodes of incontinence during the 3-day voiding diary period.	antimuscarinic medication (including narrow-angle glaucoma and urinary or gastric retention), nonpharmacological treatment for OAB including electro stimulation therapy or start of a bladder training program during the 2 weeks before or during the study, diabetic neuropathy, use of drugs intended to treat incontinence, use of any drugs with cholinergic or anticholinergic side-effects, and participation in a clinical trial within 30 days before the study entry; pregnant or nursing women, women of child-bearing potential intending to become pregnant during the study or who were not going to use reliable contraceptive methods.			
Chapple, 2004[16] Study:RCT Sample:1049	Patients with urge incontinence, frequency of micturition, and urinary urgency.	Not reported	Darifenacin	Placebo	Not reported
Choo, 2008[17] Study: H5 Sample: 357	Men and women aged ≥18 years with symptoms of OAB for ≥3months; average frequency of ≥8 voids per 24h and experienced at least three episodes of urgency or three episodes of urgency incontinence during the 3-day voiding	Clinically significant bladder outlet obstruction, a PVR volume of >200ml, incontinence for which stress was determined to be the predominant factor, presence of a neurological cause for detrusor muscle overactivity, evidence of urinary tract infection or bladder stones, previous pelvic irradiation, or previous or current malignant	Solifenacin 5mg/10mg	Tolterodine 4mg	Research grant from Astellas Pharma Inc., Tokyo, Japan

Reference Study, Sample	Inclusion Criteria	Exclusion Criteria	Active	Control	Sponsorship
	diary period	disease in the pelvic organs, any medical condition contraindicating the use of antimuscarinic medication(including narrow angle glaucoma and urinary or gastric retention), non-pharmacological treatment for OAB including electro stimulation therapy or start of a bladder training program during the 2 weeks before or during the study, diabetic neuropathy, use of drugs intended to treat incontinence, use of any drugs with cholinergic or anitcholinergic side effects and participation in a clinical trial within 30 days before study entry; women of child-bearing potential who were pregnant or nursing, intending to become pregnant during the study, or who were not using reliable contraceptive methods.			
Chu, 2009[18] Study: RCT Sample: 672	Men and women aged ≥18 years with a diagnosis of OAB made by an investigator based on symptoms (urinary frequency, urgency, or urge incontinence); had to record a mean of >=8 micturitions per 24 hours plus a mean of ≥1 incontinence episode per 24hours and/or a mean of ≥1 urgency episode per	Stress urinary incontinence or mixed urinary incontinence in which stress was predominant (mixed incontinence was otherwise allowed), a neurologic cause of detrusor overactivity, urinary retention, grade III/IV prolapse with cystocele, and recurrent or active urinary tract infection; patients with abnormal findings on 12-lead ECG or abnormal laboratory findings. Women of childbearing potential were	Solifenacin	Placebo	Funded and sponsored by Astellas Pharma Inc., Tokyo, Japan

Reference Study, Sample	Inclusion Criteria	Exclusion Criteria	Active	Control	Sponsorship
	24 hours	required to have a negative serum pregnancy test at screening and to use a medically acceptable form of contraception during study participation			
Diokno, 2003[19-22] OPERA (Overactive bladder: Performance of Extended Release Agents) trial USA N: 790	OPERA (Overactive bladder: Performance of Extended Release Agents):Women with OAB, aged 18 years and older, who documented 21 to 60 UUI episodes per week and an average of 10 or more voids per 24 hours; predominant urge UI; with or without history of prior treatment with an anticholinergic drug for OAB.	Treatable genitourinary conditions that could cause incontinence, 2 post void residual urine volumes shown by ultrasonography to exceed 150 mL; pronounced risk of developing complete urinary retention, clinically important medical problems that would put a participant at undue risk of anticholinergic effects, hematuria, uncontrolled narrow-angle glaucoma, obstructive uropathy, reduced gastrointestinal motility, and known hypersensitivity to the study medications.	Extended-release formulations of oxybutynin at 10 mg/d	Tolterodine at 4 mg/d	ALZA Corporation, Mountain View, California, and Ortho-McNeil Pharmaceutical, Raritan, NJ
Dmochowski, 2010[23] Study:RCT Sample:896	Men and women aged >=18 years with OAB symptoms for >=3 months before screening, recorded a mean of >=8 micturitions per 24 hours and >= 3 urgency episodes per 24 hours in a 3-day bladder diary at baseline, and rated their bladder condition at baseline as causing at least some moderate problems using the Patient Perception of Bladder	Patients with a history of acute urinary retention requiring catheterization, severe voiding difficulties in the judgment of the investigator, urinary incontinence symptoms attributed by the investigator primarily to stress urinary incontinence, significant pelvic organ prolapse or lower urinary tract surgery within the preceding 6 months, clinically significant hepatic or renal diseases, neurologic disease that significantly affected bladder function, treatment with an	Fesoterodine	Placebo	Funded by Pfizer, Inc.

Reference Study, Sample	Inclusion Criteria	Exclusion Criteria	Active	Control	Sponsorship
	Condition (PPBC).	antimuscarinic OAB medication or potent CYP3A4 inhibitor within 2 weeks of screening, and any contraindication to fesoterodine. Also excluded were men with intermittent or unstable use of alpha blockers or 5-alpha reductase inhibitors (consistent use was permitted) or who started such treatment within 4 weeks of screening.			
Dmochowski, 2008[24] RCT USA N: 564	Men and women aged 18 years or older with OAB of 6 months' or longer duration with symptoms of urinary frequency (a mean of 10 or more toilet voids per day), urgency (1 or more episodes of severe urgency associated with a toilet void), and UUI (a mean of 1 or more UUI episodes per day).	Total voided volumes greater than 3000 mL/day or a mean volume voided/void greater than 250 mL; predominantly stress, insensate, or overflow incontinence; history of neurogenic bladder, indwelling or intermittent catheterization, significant renal disease (defined as serum creatinine greater than 1.5 mg/dL), uninvestigated hematuria or urinary tract infection during screening, or a history of more than 3 urinary tract infections in the previous 12 months; other bladder pathologies, including clinically significant retention (defined as post void residual urine volume greater than 100 mL), cancer, and interstitial cystitis; prostate specific antigen level greater than 4 ng/mL, prostate cancer, or chronic prostatitis.	Trospium chloride 60 mg once daily	Placebo	Esprit Pharma and Indevus Pharmaceuticals Inc.

Reference Study, Sample	Inclusion Criteria	Exclusion Criteria	Active	Control	Sponsorship
Dorschner, 2000[25] RCT Country: Not reported N: 107	Men and women older than 60 years of age with urgency, urge incontinence, or mixed urge-stress incontinence, >1 episode of UI/day and micturition volume <300ml/micturition	Acute urinary tract infections, mechanical or functional bladder-emptying disorders, residual urine >20% of voided volume by ultrasound, micturition volume >300ml in uroflow, renal insufficiency, concomitant medications interfering with the drug studied (neurotropic/ musculotropic spasmolytics, centrally acting muscle relaxants, psychopharmacological agents or drugs for the treatment of Parkinson's disease, anti-arrhythmic), serious life threatening cardiovascular diseases (myocardial infarction within the previous 3 months, unstable coronary heart disease, implanted cardiac pace-maker, decompensated myocardial insufficiency, tachycardia or bradycardia at rest, second-or third-degree atrio-ventricular block, complete bundle branch interventricular heart block, chronic atrial fibrillation and ventricular extrasystoles Lown IVb in the pre-study ECG monitoring.	Propiverine (15 mg t.i.d.)	Placebo	Grant provided by Apogepha
Drutz, 1999[26] RCT United States and Canada N: 277	Age ≥18 years; all female patients were to be postmenopausal, surgically sterile, or using an adequate contraceptive method before and during the	Clinically significant stress incontinence as determined by the investigator during a cough stress test maneuver; hepatic or renal disease; any disease which the investigator thought made the patient unsuitable for inclusion;	Tolterodine 2mg b.i.d. or oxybutynin 5mg t.i.d.	Placebo	The study was funded by Pharmacia & Upjohn AB, Uppsala, Sweden

Reference Study, Sample	Inclusion Criteria	Exclusion Criteria	Active	Control	Sponsorship
	study; evidence of detrusor overactivity on subtracted cystometry (phasic detrusor contraction with an amplitude ≥10cmH_2O), along with urinary frequency (≥8 micturitions on average per 24 hours) and either urge incontinence (≥1 incontinence episode on average per 24 hours), as confirmed by micturition diaries during the run-in period, and/or urinary urgency.	recurrent urinary tract infections; interstitial cystitis; uninvestigated hematuria or hematuria secondary to malignant disease; indwelling catheter or intermittent catheterization; treatment with any investigational drug in the 2 months prior to entry; previous treatment with tolterodine; electro-stimulation therapy or bladder training within 14 days prior to entry o initiation during the study; treatment with any anticholinergic drug, or any drug for urinary urge incontinence within 14 days prior to the baseline visit or initiation during the study; unstable dosage of any treatment with anticholinergic adverse effects or initiation of such treatment during the study; previously demonstrated serious adverse effects on oxybutynin average total voided volume/24 hours of >3000 ml; or clinically significant voiding difficulty with risk of urinary retention (such as residual volume >20 ml or urine flow rate <10ml/s).			

Reference Study, Sample	Inclusion Criteria	Exclusion Criteria	Active	Control	Sponsorship
Goode, 2004[7] RCT analysis USA N: 197	Subjects were community-dwelling women aged ≥55 years who were recruited to a university based continence clinic through professional referrals and advertising. They had urge incontinence or mixed incontinence with urge as the predominant pattern. All patients were ambulatory and not demented. They had urodynamic evidence of bladder dysfunction, either detrusor overactivity (DO) or a maximal cystometric capacity ≥350 mL.	Not reported	Behavioral therapy	Oxybutynin 2.5mg/day to 5mg t.i.d. or Placebo	NIH Grant
Halaska, 2003[27] RCT Austria, Bulgaria, Czechoslovakia, Germany, Russia and Spain N: 358	Men and women >18 years of age with urge syndrome (undue frequency of micturition, nocturia, overwhelming urge, wetting), urge incontinence, urge incontinence as one component of mixed incontinence, or urge incontinence due to a neurological condition (detrusor hyperreflexia) as confirmed using urodynamic measurements.	Absolute tachycardia; closed-angle glaucoma; myasthenia gravis; severe arteriosclerosis of the cerebral vessels; stress incontinence; undue frequency of micturition due to heart failure, renal failure or diuretic therapy; Bladder outlet obstruction; Acute urinary tract infection at the beginning of the trial; Hiatus hernia in combination with reflux esophagitis; stenoses in the gastrointestinal tract; megacolon; colonic ulceration; allergy or intolerance towards atropine,	Trospium chloride (20 mg twice daily) or	Oxybutynin (5 mg twice daily).	Not reported

Reference Study, Sample	Inclusion Criteria	Exclusion Criteria	Active	Control	Sponsorship
		OXY, TCI or other constituents of the trial medication; concurrent medication with anticholinergics, tricyclic or tetracyclic antidepressants, a-blockers or b-sympathomimetics within the last 7 days before starting the trial; urological or gynecological operations within the last 3 months before starting the trial; serious illnesses or conditions which would preclude participation in any clinical trial (malignant neoplasms, alcoholism, drug misuse); pregnancy or lactation; participation in any other study.			
Herschorn, 2010[28] Study:RCT Sample:1712	Men and women aged ≥18 years, with symptoms of OAB (self-assessed) for ≥3 months before screening and a mean of one or more UUI episode/24 h and ≥ 8 voids/24 h reported in 3-day bladder diaries completed at baseline.	Patients with clinically significant hepatic or renal disease; lower genitourinary pathology or surgical treatment thereof responsible for voiding dysfunction; neurological conditions such as stroke, multiple sclerosis, spinal cord injury, or Parkinson's disease; previous history of acute urinary retention requiring catheterization; symptoms of incontinence being predominately stress UI in the opinion of the investigator; treatment with antimuscarinic OAB medication within 2 weeks before screening; or use of any electrostimulation,	Fesoterodine	Placebo	Sponsored by Pfizer Inc.Editorial assistance was provided by Simon J. Slater, PhD and Colin P.Mitchell, PhD from Complete Healthcare Communications, Inc. and was funded by Pfizer Inc.

Reference Study, Sample	Inclusion Criteria	Exclusion Criteria	Active	Control	Sponsorship
		bladder training, or pelvic floor exercises within 4 weeks of screening. Female patients of childbearing potential who were heterosexually active without using an adequate form of contraception, or who were pregnant, nursing, or with a positive urine pregnancy test were also excluded.			
Herschorn, 2008[29] Study: RCT Sample: 617	≥18 years of age; mean of ≥8 micturitions per 24 hours and ≥3 episodes of urgency or urgency urinary incontinence (UUI) in a 3-day bladder diary before randomization; experienced OAB symptoms for ≥3 months and at least moderate problems associated with their most bothersome OAB symptom, as reported on the OAB Bother Rating Scale	If received any drug used to treat UUI or OAB within 14 days before the study treatment period	Tolterodine-ER	Placebo	Funded by Pfizer Inc
Hill, 2006[30] Darifenacin Study Group. Country: Not reported N: 439	Male and female patients, aged >18 years, with urge incontinence (>10 episodes over 14 days), high micturition frequency (mean of >8 eight voids per day), and urinary urgency (a strong desire to void on average at least once per day) for at least 6	Clinically significant stress incontinence, bladder outlet obstruction or a postvoid residual urinary volume >200 ml; local pathology that could cause urinary symptoms (e.g., interstitial cystitis, bladder stones, severe constipation (≤2 bowel movements per week), history of intermittent urinary tract infections; those who had undergone urogenital	Darifenacin (Novartis Pharma AG, Basel, Switzerland) once-daily 7.5, 15, 30 mg	Placebo	The study was funded by Pfizer Inc.

Reference Study, Sample	Inclusion Criteria	Exclusion Criteria	Active	Control	Sponsorship
	months, regardless of previous antimuscarinic treatment.	surgery within the previous 6 months, or cystoscopy in the previous 30 days; patients with indwelling catheter or using intermittent self-catheterization; presence of clinically significant systemic disease; patients who intended to start a bladder-training program during the study, or had contraindications to antimuscarinic therapy; pregnant and lactating women; no concomitant treatment with drugs (including drugs with significant anticholinergic effects), opioids, hormone replacement therapy (unless taken for >2 months), and drugs known to be significant inhibitors of cytochrome P450 2D6 or 3A4 isoenzymes (cimetidine, fluoxetine, ketoconazole, itraconazole, etc.).			
Homma, 2003[31-33] Japanese and Korean Tolterodine Study Group Korea and Japan N: 608	Men and women aged >20 years with symptoms of urinary urgency, urinary frequency (> 8 voids/24 hours), urge incontinence (>5 episodes/ week) and symptoms of OAB for >6 months were eligible for inclusion. Patients were recruited based solely on their symptoms of OAB, irrespective of	Demonstrable stress incontinence; total daily urine volume of >3 L; average volume voided/ void of >200 mL; significant hepatic or renal disease; any contraindication to anticholinergic treatment, e.g. uncontrolled narrow-angled glaucoma, urinary retention or gastric retention; symptomatic or recurrent UTI; interstitial cystitis; haematuria or BOO; an indwelling catheter or	Tolterodine 4mg capsules once daily	Oxybutynin 3mg tablets three times daily, placebo	This study was supported by a grant from Pharmacia Corporation.

Reference Study, Sample	Inclusion Criteria	Exclusion Criteria	Active	Control	Sponsorship
	whether they had received previous antimuscarinic treatment and irrespective of their response to such therapy.	intermittent self-catheterization; and electro-stimulation or bladder training within 14 days before randomization or expected to commence during the study period; pregnant or nursing women and women of childbearing potential not using reliable contraception.			
Jacquetin, 2001[34] RCT Belgium and France N: 251	Male and female patients aged ≥18 years were eligible for inclusion in the study if they had urodynamically proven overactive bladder, and symptoms of urgency and/or urge incontinence (≥1 incontinence episode/24 hours) with increased frequency of micturition (≥8 micturitions/24 hours) irrespective of prior treatment or treatment failure.	Significant stress incontinence; hepatic or renal disease; symptomatic or recurrent urinary tract infection (UTI); interstitial cystitis; haematuria; clinically significant voiding difficulty; patients receiving bladder training, electro-stimulation therapy or having an indwelling catheter or on intermittent catheterization; pregnant or nursing women, or women of childbearing age who were not using reliable contraception.	Tolterodine 1 or 2mg twice daily	Placebo	Pharmacia Corporation
Johnson, 2005[35] RCT analysis USA N: 131	To be included in the study, participants had to report at least two accidents per week and to demonstrate the ability to complete an interpretable bladder diary that confirmed this frequency of urine loss. Urge incontinence had to	Participants with continual leakage, elevated postvoid residual urine volume (4200 mL), narrow angle glaucoma, uterine prolapse past the vaginal introitus, unstable angina pectoris, decompensated congestive heart failure, or impaired mental status (MMSE score 20) were excluded.	Behavioral training, drug treatment (oxybutynin IR titrated from 2.5 mg per day to 5.0 mg three times a day)	Placebo	Supported by grant from the National Institute on Aging. Dr. Johnson received additional support from the Emory University Center for Health in Aging. The John A. Hartford Foundation Southeast Center of Excellence in Geriatric Medicine and the Birmingham/

Reference Study, Sample	Inclusion Criteria	Exclusion Criteria	Active	Control	Sponsorship
	be the predominant pattern (urge accidents exceeded the number of stress and other accidents), with urodynamic evidence of bladder dysfunction. Two-channel supine water cystometry was performed to demonstrate detrusor instability (defined as urodynamic observation of involuntary detrusor contractions during the filling phase) or sensory urgency (defined as bladder capacity of less than 350 mL) for inclusion in the study.				Alabama VA GRECC provided infrastructural support that enabled this inter-institutional collaboration.
Junemann, 2000[36] Study: RCT Sample: 234	Patients with urge - syndrome (motor urge, sensory urge and combined motor urge and stress incontinence). Patients medical history and a urodynamic measurement (minimum one unstable detrusor contraction of 10 cm H2O or first desire to void at a bladder filling of <150ml) verified the diagnosis of urge-syndrome	NR	Trospium hydrochloride	Tolterodine and placebo	NR

Reference Study, Sample	Inclusion Criteria	Exclusion Criteria	Active	Control	Sponsorship
Kaplan, 2010[37,38] Study: RCT Sample: 2417	Subjects with OAB symptoms for >=months and recorded micturitions and >=1 urgency urinary incontinence episode per 24h in 3-day baseline diaries	NR	Fesoterodine	Tolterodine/Placebo	Sponsored by Pfizer Inc.
Karram, 2009[39,40] Study: VENUS Sample: 739	This study, that is, the VENUS study enrolled patients aged>=18 years with OAB (at least 1 urgency episode with or without incontinence and >=8 micturitions per 24 hours) for >=3 months	Presence of stress or stress-predominant mixed urinary incontinence, chronic inflammation or cystitis, and clinically significant bladder outlet obstruction	Solifenacin	Placebo	Research grant from Astellas Pharma US, Inc. and GlaxoSmithKline
Kelleher, 2002[41-48] RCT USA N: 1015	Male and female patients aged 18 years or older with urinary frequency (average of ≥8 micturitions/24 hours over a 7-day period), urge incontinence (≥5 episodes/week), and symptoms of OAB for at least 6 months.	Other types of bladder dysfunction, with diseases that may have affected urinary output.	Tolterodine extended-release (ER) 4 mg once/day, or tolterodine immediate-release (IR) 2 mg twice daily	Placebo	Pharmacia Corporation
Khullar, 2004[49,50] RCT UK N: 854	Women 18 years or older with urge-predominant mixed incontinence, including urge incontinence (five or more episodes per week), urinary frequency (eight or more micturitions on average in 24 hours), and urgency in combination with	Pure stress urinary incontinence; predominant stress urinary incontinence; a total daily urine volume greater than 3 L; suspected or documented hepatic or renal dysfunction; symptomatic urinary tract infection; interstitial cystitis, uninvestigated hematuria, or clinically significant bladder obstruction; any contraindication to	Tolterodine tartrate extended-release (ER) 4 mg	Placebo	Pfizer Inc

Reference Study, Sample	Inclusion Criteria	Exclusion Criteria	Active	Control	Sponsorship
	stress incontinence irrespective of the use of previous antimuscarinic treatment.	antimuscarinic treatment; and any nonsurgical treatment for incontinence within 4 weeks of the first study visit; treatment within 2 weeks before randomization with any drug for incontinence (except estrogen therapy started more than 2 months before the first visit); agonist or potent inhibitors of cytochrome P450 3A4 isoenzymes; pregnancy, lactation, or inadequate contraception.			
Lee, 2010[51] Study: Propiverine study on overactive bladder including urgency data N: 264	Men and women ages ≥18 years who had self-reported symptoms of OAB for ≥3months; average urinary frequency of ≥10 voids/24h and urgency of two or more episodes/24h defined as 'moderate to severe' in the Indevus Urgency Severity Scale(IUSS) during the 3-day voiding diary period before randomization	Clinically significant stress urinary incontinence (more than one episode per week); genitourinary conditions that could cause OAB symptoms, such as UTI; and contraindications to the use of antimuscarinic drugs	Propiverine hydrochloride 60 mg/d	Placebo	Sponsored by Jeil Pharmaceutical Co. Ltd., Seoul, Korea
Lee, 2002[52] RCT South Korea N: 228	Male and female subjects aged ≥18 years with symptoms of overactive bladder for ≥6 months were eligible for enrolment in the study. Symptoms, as measured by micturition diaries, were defined as urinary urgency and	(i) significant stress incontinence; (ii) women of childbearing age who were not using reliable contraception; (iii) pregnant or nursing women; (iv) treatment with any drug with known anticholinergic side-effects in the in the 2 weeks prior to the study; (v) significant renal or hepatic disease; (vi) any	Tolterodine 2mg bid	Oxybutynin 5mg bid	Grant from Pharmacia

Reference Study, Sample	Inclusion Criteria	Exclusion Criteria	Active	Control	Sponsorship
	frequency (≥8 micturitions on average per 24 hours), with or without urge incontinence. Patients were enrolled exclusively on the basis of symptoms (i.e. urodynamics was not performed), irrespective of whether they had received prior antimuscarinic therapy.	contraindication to antimuscarinic therapy (e.g. narrow-angle glaucoma, urinary or gastric retention, known hypersensitivity to tolterodine or oxybutynin); (vii) symptomatic acute or recurrent urinary tract infection; (viii) interstitial cystitis or hematuria; (ix) bladder outlet obstruction; and (x) patients receiving bladder training, electro-stimulation therapy or having an indwelling catheter or on intermittent catheterization.			
Lehtoranta, 2002[53] RCT Finland N: 9	Female or male patients aged 18–75 years were recruited to the study. They had to have a history of urgency or urge incontinence and cystometrically proven detrusor hyperreflexia or instability according to the ICS criteria (International Continence Society).	Stress incontinence and pure nocturnal enuresis were excluded.	Oxybutynin 5mg/30ml three times daily	Placebo(30ml of sterile saline)	Not reported
Madersbacher, 1999[54] RCT USA N: 366	History of urgency or urge incontinence, a maximum cystometric bladder capacity of ≤300 ml, age ≥18years and body weight ≥45kg.	Detrusor hyperreflexia, postoperative (bladder) incontinence, intravesical obstruction, a postvoid residual urine (PVR) of >15% of the maximal cystometric bladder capacity, acute UTIs, angina pectoris, glaucoma, megacolon, clinically relevant cardiac, renal or hepatic dysfunctions, tachy/dysrhythmias, frequency or nocturia due to heart or	Propiverine 15mg three times a day	Oxybutynin 5mg twice a day, placebo three times a day	Not reported

Reference Study, Sample	Inclusion Criteria	Exclusion Criteria	Active	Control	Sponsorship
		renal insufficiency, or overt cerebral sclerosis.			
Malone-Lee, 2009[55] RCT UK N: 307	Male and female subjects aged ≥18 years with urinary frequency (defined as an average of ≥8 voids/24 hours, measured over a 7-day period) and urgency (with or without UUI), symptoms of OAB for ≥6 months before randomization, with no significant stress UI and adequate contraception.	Mean volume voided of >300 mL/void or a mean total volume of urine >3000 mL/24 hours; significant hepatic or renal disease, symptomatic UTI, diagnosed interstitial cystitis, un-investigated hematuria, or clinically significant BOO; anticholinergic drugs or other treatments for OAB in the 14 days before randomization; known hypersensitivity to tolterodine-ER or any of its excipients; oral cytochrome P450 3A4 inhibitors (e.g. macrolide antibiotics), and electro-stimulation or bladder retraining in the 3 months before randomization.	Tolterodine-ER (4 mg capsule od)	Placebo	Pharmacia (now Pfizer Ltd)
Malone-Lee, 2001[56] RCT United Kingdom, France, and the Republic of Ireland N: 177	Older men and women (age ≥65 years) with symptoms of urinary urgency, increased frequency of micturition (≥8 micturitions/24 hours), and/or urge incontinence (≥1 episode/24 hours).	Significant stress incontinence, urinary outflow obstruction, urinary retention (as determined by palpation after voiding), symptomatic urinary infection, interstitial cystitis, unexplained hematuria, use of urinary catheterization or electro-stimulation, hepatic and renal disease with biochemical markers twice the upper limit of the normal reference range, concomitant antimuscarinic medication, previous treatment with tolterodine, and exposure to any other investigational drug in the preceding 2 months.	Tolterodine 1 mg or 2 mg twice daily	Placebo	Pharmacia & Upjohn AB

Reference Study, Sample	Inclusion Criteria	Exclusion Criteria	Active	Control	Sponsorship
Moore, 1990[57] Study: RCT Sample: 53	Patients with involuntary detrusor contractions >30cm H2O during the filling phase of cystometry	Those with neurological and other urological disorders; patients with coexistent genuine stress incontinence, low compliance bladder, bacterial or interstitial cystitis, age greater than 75 years or previous treatment with oxybutynin	Oxybutynin hydrochloride	Placebo	Tillots Laboratories provided oxybutynin and placebo tablets
NCT00444925[58] Study: RCT N: 1712	Adult overactive bladder (OAB) patients who present with OAB symptoms, including urinary frequency ≥ 8 per day and urgency urinary incontinence ≥1 per day	Patients with conditions that would contraindicate for fesoterodine use, e.g., hypersensitivity to the active substance (fesoterodine) or to peanut or soya, urinary retention, and gastric retention; patients with significant hepatic and renal disease or other significant unstable diseases; and OAB symptoms caused by neurological conditions, known pathologies of urinary tract, etc.	Fesoterodine	Tolterodine/Placebo	Sponsored by Pfizer Inc.
Rentzhog, 1998[59] Study: RCT Sample: 81	Men and women aged 18-75 years; presence of symptoms of urinary urgency, increased frequency of micturitio (at least 8 micturitions per 24 hours) and/or urge incontinence (at least one episode of incontinence per 24 hours) during a 1-weel pre-study run-in perioc All eligible patients should have had urodynamically confirmed detrusor instability (defined as a phasic increase in	Stress incontinence or detrusor hyperreflexia; clinically significant cardiac, hepatic, renal or hematological disorders; patients with contraindications to antimuscarinic agents; and pregnant or lactating women and women of childbearing age who were not using reliable contraception.	tolterodine	Placebo	Pharmacia and Upjohn AB, Uppsala. Sweden

Reference Study, Sample	Inclusion Criteria	Exclusion Criteria	Active	Control	Sponsorship
	detrusor pressure in the presence of typical symptoms) and a maximum urinary flow rate (Q max)of >=15mL/s (patients with a lower Qmax were eligible for inclusion provided there was no evidence of clinically significant bladder outlet obstruction), either sterile urine or clinically insignificant bacteriuria, and normal routine laboratory tests				
Rogers, 2009[60-62] Study: RCT Sample: 413	Women ≥18 years with OAB symptoms for>=3 months; mean of >=8 micturitions per 24 hours, including ≥0.6 UUI episodes and ≥3 OAB micturitions (i.e. micturitions associated with at least a moderate degree of urgency), in a 5-day bladder diary at baseline; subjects also reported being in a stable, sexually active relationship (self-defined) for ≥6 months and having at least some moderate problems related to their bladder condition on the Patient Perception of Bladder Condition.	One subject in the tolterodine group with an extreme increase in the number of UUI episodes per 24 hours from baseline to week 12 was identified as an influential outlier and was excluded from all efficacy analyses	Tolterodine-ER	Placebo	Funded by Pfizer Inc.

Reference Study, Sample	Inclusion Criteria	Exclusion Criteria	Active	Control	Sponsorship
	Heterosexual.				
Rogers, 2008[61] RCT USA N: 413	Women (aged ≥18 years) with a mean of greater than or equal to eight micturitions, ≥0.6 UUI episodes, and greater than or equal to three OAB micturitions (i.e., micturitions associated with moderate or severe urgency or UUI) per 24 hours with at least "some moderate problems" on the Patient Perception of Bladder Condition Questionnaire ; with OAB symptoms for ≥3 months and to have been in a stable, sexually active relationship (self-defined) with a male partner for ≥6 months.	Stage ≥3 pelvic organ prolapse, history of lower urinary tract surgery, lifelong sexual dysfunction unrelated to lifelong UUI, or predominant stress UI.	Tolterodine ER (4 mg)	Placebo	Pfizer Inc
Rudy, 2006[63] RCT analysis USA N: 658	Men and women ≥18 years old with OAB symptoms for ≥6 months, a minimum urinary frequency of 70 toilet voids per 7 days (i.e. mean ≥10 voids/day), and symptoms of urgency ; with at least seven UUI episodes/week.	Predominately stress, insensate, or overflow; neurogenic bladder disorders, significant renal disease, uninvestigated haematuria, >2 UTIs during the previous year; significant BOO, concurrent anticholinergic drug use or other drug therapy for OAB within 21 days before randomization, bladder surgery within 6 months, cancer, interstitial cystitis, men with PSA levels of ≥10 ng/mL, diuretic use, estrogen	Trospium chloride 20 mg twice daily	Placebo	Indevus Pharmaceuticals

Reference Study, Sample	Inclusion Criteria	Exclusion Criteria	Active	Control	Sponsorship
		therapy, and non-pharmacological bladder therapy that were not part of a stable, long-term program.			
Sand, 2009[9,64,65] Pooled USA N: 1971	Men and women ≥18 years of age who reported OAB symptoms for ≥6 months and demonstrated urinary frequency (≥8 micturitions per 24 hours) and either urinary urgency (≥6 total episodes) or UUI (≥3 total episodes) in 3-day bladder diaries at least moderate bladder problems on a six-point Likert scale: "My bladder causes me no problems (0), very minor problems (1), minor problems (2), moderate problems (3), severe problems (4), or very severe problems (5)."	Lower urinary tract pathology that could (in the investigator's opinion) be responsible for urgency or incontinence, significant pelvic prolapse (grade III or higher), clinically relevant bladder outlet obstruction, polyuria (>3 L/24 hours), symptomatic or recurrent urinary tract infections, postvoid residual volume >100 mL, and recent treatment with an antimuscarinic agent.	Fesoterodine 4 or 8 mg, or tolterodine extended release (ER) 4 mg	Placebo	Schwarz Bio- Sciences GmbH and Pfizer Inc.
Sand, 2009[66] Dmochowski, 2010[67] Pooled Country not reported N: 989	Subgroup analysis of women aged ≥18 years with OAB of ≥6 months' duration with urinary urgency (≥1 severe urgency severity rating on the validated Indevus urgency severity scale); urinary frequency (average ≥10 voids/day, occurring at any time	Predominantly stress, insensate, or overflow incontinence (as determined by investigators), demonstrable renal or urinary disorders including neurogenic bladder disorders, significant renal disease, uninvestigated hematuria, current or a history of ≥3 episodes of urinary tract infection in the preceding year, bladder	Trospium ER (60-mg capsules)	Placebo	Allergan, Inc. and Endo Pharmaceuticals (formerly Indevus Pharmaceuticals Inc.).

Reference Study, Sample	Inclusion Criteria	Exclusion Criteria	Active	Control	Sponsorship
	of the 24-hour period); and pure urge or mixed urinary incontinence with predominant UUI, with an average of ≥1 UUI episode/day.	outlet obstruction, interstitial cystitis, or bladder cancer; subjects requiring long-term diuretic or estrogen therapy.			
Staskin, 2006[68] Pooled Country not reported N: 3298	Pooled analysis of 4 RCTs of men and women over 18 years with OAB (mean of ≥8 voids/24 hours, plus ≥1 incontinence episode or ≥1 urgency episode/24 hours)	Women with a history of stress-predominant UI, positive cough-provocation test; no baseline assessment or no episodes of the individual diary symptom during the baseline diary screening period.	Solifenacin 5mg; Solifenacin 10mg;	Placebo	Yamanouchi Pharma Inc.
Staskin, 2007[69] Trospium Study Group. USA N: 601	Not reported	Not reported	Trospium chloride 60 mg/day	Placebo	Esprit Pharma and Indevus Pharmaceuticals
Staskin, 2004[70] RCT USA N: 658	Not reported	Not reported	Trospium chloride 20-mg twice daily	Placebo	Not reported
Staskin, 2009[71] RCT US N: 789	Men and women with OAB who were 18 years or older; urge or mixed UI with a predominance of urge UI episodes as well as a mean of 8 or more urinary voids per day and 4 or more urge UI episodes per day on a baseline 3-day bladder diary regardless of whether symptoms were of neurological origin. The bladder diary was to be independently completed by the patient. Patients	Potential participants were excluded from study based on criteria designed to rule out incontinence related to chronic illness, anatomical abnormality and concomitant medication.	OTG (oxybutynin chloride)	Placebo	Laboratory assessments were performed at Mayo Laboratory for Clinical Trials, Rochester, Minnesota

Reference Study, Sample	Inclusion Criteria	Exclusion Criteria	Active	Control	Sponsorship
	needed to have a mean voided volume of 350 ml or less during a 2-day urine collection period and a PVR of 250 ml or less on ultra-sonography or catheterization.				
Steers, 2005[72] RCT Canada, USA N: 395	Patients aged >18 years with symptoms of OAB for at least 6 months, capable of independent toileting. Irrespective of response to previous treatments patients had to have urge incontinence (>5 episodes per week), voiding frequency (>8 voids per day), and urgency (a strong desire to void at least once per day). Adequate method of contraception throughout the study for young women.	Contraindications to anticholinergic therapy (e.g., uncontrolled narrow-angle glaucoma, urinary retention or gastric retention); clinically significant stress incontinence, BOO and/or a postvoid residual urinary volume (PVR) of >200 mL ; pregnancy and lactation; genitourinary conditions that could cause urinary symptoms; fecal impaction or severe constipation (two or fewer bowel movements per week); urogenital surgery within the previous 6 months; bladder biopsy in the previous 30 days; indwelling catheter and intermittent self-catheterization; clinically significant disease; bladder-training program during the study; concomitant treatment with anticholinergic or antispasmodic drugs (including drugs with significant anticholinergic effects, e.g., imipramine), opioids and other drugs known to cause significant constipation, hormone replacement therapy (unless	Darifenacin controlled-release tablets 7.5 mg	Placebo	This study was funded by Pfizer Inc.

Reference Study, Sample	Inclusion Criteria	Exclusion Criteria	Active	Control	Sponsorship
		taken for >2 months), and drugs known to be potent cytochrome P450 3A4 inhibitors (e.g., ketoconazole).			
Szonyi, 1995[73] RCT Country not reported N: 60	Outpatients of either sex aged over 70 with symptoms of urinary frequency, urgency an urge incontinence wer recruited. Patients had to be mobile, able to attend an outpatient department, able to keep a diary chart and willing to give consent.	Urinary infections at the time of recruitment, patients with severe hepatic or renal disease, glaucoma, or uncontrolled diabetes. Patients on concomitant anticholinergic therapy with imipramine were excluded.	Oxybutynin 2.5 mg twice daily	Placebo	Funded by Smith and Nephew Pharmaceuticals Ltd.
Thuroff, 1991[74] Study: RCT N: 169	15 years old and older complaining of symptoms of frequency, urgency and/or incontinence, ir whom cystometry findings were related to detrusor hyperactivity, whether idiopathic (unstable detrusor) or neurogenic (detrusor hyperreflexia) in origin	Pregnancy, congestive heart failure, severe renal/liver disease, myasthenia gravis, unable to swallow/uncooperative patient, hiatal hernia/reflux esophagitis, gastrointestinal tract obstruction, urinary tract obstruction, residual urine greater than 50ml, untreated urinary tract infection and hyperreflexia without urge	Oxybutynin chloride	Propantheline and placebo	Pharmcia Leo Therapeutics, Helsingborg, Sweden provided the pharmaceutical preparations used in this study
Toglia, 2010[75] Study: Post-hoc Karram, 2009[39] VENUS N: 739	Patients aged ≥18 years with OAB symptoms for ≥3 months	Reported previously-18995887	Solifenacin	Placebo	Supported by Astellas Pharma US, Inc. and GlaxoSmithkline
U.S. Food and Drug Administration[76] Cardozo, 2008[77] Study: SUNRISE N: 865	Male of female aged ≥18 years, from whom written consent had been obtained, and who were willing and able to complete a voiding diary correctly; symptoms	NR	Solifenacin	Placebo	Research grant from Astellas Pharma Europe Ltd.

Reference Study, Sample	Inclusion Criteria	Exclusion Criteria	Active	Control	Sponsorship
	of OAB (including urinary frequency, urgency or urgency incontinence) for ≥3 months and three or more episodes of urgency with or without incontinence in the last 3 days				
U.S. Food and Drug Administration, 2004[78] Study: RCT Sample: 680	Male and female subjects, aged 18 years and older with symptoms of overactive bladder for at least 6 months. Subjects must exhibit all of the following symptoms of overactive bladder during the run-in period: 1) incontinence 2) frequency of micturition -at least 8 times per 24 hours, on average, over the run-in period 3) urgency - at least once per 24 hours, on average, over the run-in period		Darifenacin	Placebo	NR
U.S. Food and Drug Administration, 2004[79] Study: RCT N: 562	Male and female subjects, aged 18 years and older with symptoms of overactive bladder for at least 6 months. Subjects must exhibit all of the following symptoms of overactive bladder during the run-in period: 1) incontinence 2)		Darifenacin	Placebo	NR

Reference Study, Sample	Inclusion Criteria	Exclusion Criteria	Active	Control	Sponsorship
	frequency of micturition -at least 8 times per 24 hours, on average, over the run-in period 3) urgency -at least once per 24 hours, on average, over the run-in period				
U.S. Food and Drug Administration, 2007[80] Study: RCT N: 601	Patients currently undergoing OAB therapy at the time of enrollment were required to undergo 7-day wash-out period, followed by 3-day baseline urinary diary collection, prior to randomization. Patients not under OAB therapy could begin treatment after 3-days of baseline diary collection	NR	Trospium chloride ER	Placebo	Indevus Pharmaceuticals, Inc.
U.S. Food and Drug Administration, 2007[81] Study: RCT N: 564	Patients currently undergoing OAB therapy at the time of enrollment were required to undergo 7-day wash-out period, followed by 3-day baseline urinary diary collection, prior to randomization. Patients not under OAB therapy could begin treatment after 3-days of baseline diary collection	NR	Trospium chloride ER	Placebo	Indevus Pharmaceuticals, Inc.
Chapple, 2005, 2007[82-84] U.S. Food and Drug Administration(905-EC-001)	The STAR study :men and women aged at least 18 years who	Stress incontinence or mixed incontinence where stress was predominant (mixed	Solifenacin 5 mg	Tolterodine ER 4 mg	Grant from Yamanouchi Pharmaceutical Co, Ltd

Reference Study, Sample	Inclusion Criteria	Exclusion Criteria	Active	Control	Sponsorship
STAR study group Country: not reported N: 1,177	had OAB symptoms (including urinary frequency, urgency or urgency incontinence) for 3 months or more; with an average of >8 micturitions/day; >1 incontinence episode/day, or an average of >1 urgency episode/day.	incontinence was allowed otherwise) and patients with a neurological cause of abnormal detrusor activity.			(now Astellas Pharma Inc). Tokyo, Japan.
Vardy, 2009[85] Study: RCT VIBRANT Sample: 768	Eligible patients (aged ≥18 years) were required to have OAB symptoms for ≥3 months (≥8 micturitions and ≥1 urgency episode, with or without incontinence, per 24 hours) and a PPBC score ≥3	Significant stress or stress-predominant mixed incontinence, recurrent urinary tract infection (UTI; ≥3 episodes within the past 3 months) or evidence of UTI at baseline, evidence of chronic urologic inflammation/interstitial cystitis or urinary/gastric retention.	Solifenacin	Placebo	Research grant from Astellas Pharma U.S. Inc. and Glaxo-Smithkline
Wang, 2006[86] RCT Taiwan N: 74	Age: 16 to 80 years; OAB for more than 6 months. No patients had taken anticholinergics or tricyclic antidepressants and none had been treated with pelvic floor muscle training, bladder training, or pelvic prolapse repair.	Pregnancy, neurologic disorders, diabetes mellitus, demand cardiac pacemaker or intrauterine device use, genital prolapse greater than Stage II of the International Continence Society grading system, a postvoid residual urine volume greater than 100 mL, overt urinary stress incontinence, a history of any incontinence surgery, and urinary tract infection.	Electrical stimulation (ES)	Oxybutynin, placebo	Grant from National Science Council, Taiwan.
Yamaguchi, 2007 [87] Study: RCT N: 1593	Men and women aged ≥20 years and with symptoms of OAB reported for ≥6 months were eligible for screening and study enrolment. To	Significant BOO, an assessment based on measuring the postvoid residual urine volume(PVR); patients with a PVR of ≥100mL; presence of BOO symptoms assessed by	Solifenacin 5mg or 10mg	Propiverine or placebo	Funded and sponsored by Astellas Pharma Inc.(formerly Yamanouchi Pharmaceutical Co. Ltd), Tokyo, Japan

Reference Study, Sample	Inclusion Criteria	Exclusion Criteria	Active	Control	Sponsorship
	be eligible for randomization after the 2-week placebo run-in period, patients had to report a mean number of voids/24 hr of ≥8, ≥3 episodes of urgency and/or ≥3 episodes of urgency incontinence during a 3-day voiding -diary period.	investigators(who were all urologists); urinary retention, demonstrable stress incontinence, bladder stones, UTI, interstitial cystitis, previous or current malignant disease of the pelvic organs; those taking concomitant anticholinergic medications; known hypersensitivity to anticholinergic medications or lactose.			
Zellner, 2009[88,89] Study: RCT N: 1659	Male or female outpatients aged ≥18 years with urinary frequency ≥8 micturitions per day) and urge incontinence (≥5 episodes per week), as verified in the micturition diary.	Patients were excluded if they did not complete the micturition diary correctly for 7 consecutive days to confirm that they met the inclusion criteria and to establish baseline symptoms and urgency severity before the entrance visit. Based on this diary, patients with a total daily urine volume ≥2.8 L (determined by total daily urine for 2 days, divided by 2), a mean micturition volume of >250 mL, and/or a clinically significant bladder outlet obstruction (i.e., postvoid residual urine volume of >100 mL, determined via sonography) were also excluded as were those with an indwelling catheter or intermittent self-catheterization. Those with other significant medical problems or urogenital conditions, including urinary tract infection at the screening visit (or before or at the entrance visit), interstitial	Oxybutynin Hydrochloride	Trospium Chloride	Dr. R. Pfleger GmbH (Bamberg, Germany) sponsored this study. Petra Schwantes, PhD, Biomedical Services, assisted with the writing of this article; she received compensation from the sponsor.

Reference Study, Sample	Inclusion Criteria	Exclusion Criteria	Active	Control	Sponsorship
		cystitis and/or hematuria (as determined via urinalysis), contraindications to anticholinergic therapy (e.g., untreated narrow-angle glaucoma, mechanical gastrointestinal stenosis, myasthenia gravis syndrome), tachycardiac arrhythmia, severe psychiatric illnesses, or hypersensitivity to trospium chloride or oxybutynin or 1 of the vehicle ingredients, were also excluded. Patients who had participated in a bladder-training program, or in another study within 30 days before screening, were also prohibited, as were those undergoing electro stimulation programs. Further reasons for exclusion were alcohol and/or drug abuse, pregnancy, breastfeeding, and insufficient contraception among women of childbearing age.			
Zinner, 2005[90] RCT US N: 76	Males and non-pregnant (nor breastfeeding) females aged 18–85 years with urge incontinence (>4 significant incontinent episodes per week, where significant was defined as leakage that would normally require a change of clothing or absorbent pad) and urinary frequency (≥8 voids per day, on average).	Neurogenic bladder or stress incontinence, contraindications to antimuscarinic therapy, previous bladder or prostate surgery, bladder stones (as demonstrated by pelvic x-ray or ultrasound), acute or chronic urinary tract infection, significant urinary outflow obstruction, and clinically significant concomitant disease; Patients intending to start or modify either an existing bladder training program or existing treatment	Darifenacin controlled-release tablets 15 mg and 30 mg once/daily	Oxybutynin 5 mg three times daily, Placebo	Industry and grant

Reference Study, Sample	Inclusion Criteria	Exclusion Criteria	Active	Control	Sponsorship
		with thyroid or estrogen hormone replacement therapy; those who had received treatment with drugs that affect bladder function/urine production in the previous 2 weeks.			
Zinner, 2006[91] RCT Country not reported N: 445	Men and women aged >18 years with a history of OAB for >6 months and on average >1 urge incontinence episodes/day; >8 micturitions/day; >4 urgency episodes/day and mean warning time of <15 minutes during 12 consecutive hours.	Stress urinary incontinence; marked cystocele or pelvic prolapse; those taking the following drugs in the 2 weeks prior to the screening visit: anticholinergic/antispasmodic drugs, or those with anticholinergic effects, cholinergic agonists, potent cytochrome P450 3A4 inhibitors, opioids and drugs that cause significant constipation; those who have contraindications to anticholinergic drugs, clinically significant bladder outlet obstruction, have the intention to start a bladder training program and an indwelling catheter or intermittent self-catheterization.	Darifenacin 15 mg controlled release qd	Placebo	This study was funded by Novartis Pharma AG
Zinner, 2004[92] Trospium Study Group. USA N: 523	The Trospium Study Group: male and female 18 years or older with OAB symptoms for at least 6 months; with urinary urgency, a minimum voiding frequency of 70 voids per week with at least 7 urge incontinence episodes per week.	Predominantly stress UI , insensate or overflow in nature; with neurogenic bladder disorders, significant renal disease, uninvestigated hematuria and urinary tract infection at washout or more than twice during the prior year; significant bladder outlet obstruction (post-void residual volume >100 ml); concurrent use of any anticholinergic drug or other drug therapy for overactive bladder within 21	20 mg trospium twice daily	Placebo	Indevus Corporation

Reference Study, Sample	Inclusion Criteria	Exclusion Criteria	Active	Control	Sponsorship
		days before randomization, history of bladder surgery within 6 months before randomization, bladder cancer or interstitial cystitis were excluded from study; diuretic use, estrogen therapy and nonmedical bladder therapy that was not part of a stable, long-term program.			

References for Appendix C

1. Abrams P, Freeman R, Anderstrom C, et al. Tolterodine, a new antimuscarinic agent: as effective but better tolerated than oxybutynin in patients with an overactive bladder. Br J Urol. 1998 Jun;81(6):801-10. PMID 9666761.
2. Appell RA. Clinical efficacy and safety of tolterodine in the treatment of overactive bladder: a pooled analysis. Urology. 1997 Dec;50(6A Suppl):90-6; discussion 7-9. PMID 9426760.
3. Appell RA, Sand P, Dmochowski R, et al. Prospective randomized controlled trial of extended-release oxybutynin chloride and tolterodine tartrate in the treatment of overactive bladder: results of the OBJECT Study. Mayo Clin Proc. 2001 Apr;76(4):358-63. PMID 11322350.
4. Sand PK, Miklos J, Ritter H, et al. A comparison of extended-release oxybutynin and tolterodine for treatment of overactive bladder in women. Int Urogynecol J Pelvic Floor Dysfunct. 2004 Jul-Aug;15(4):243-8. PMID 15517668.
5. Burgio KL, Locher JL, Goode PS, et al. Behavioral vs drug treatment for urge urinary incontinence in older women: a randomized controlled trial. JAMA. 1998 Dec 16;280(23):1995-2000. PMID 9863850.
6. Goode PS, Burgio KL, Locher JL, et al. Urodynamic changes associated with behavioral and drug treatment of urge incontinence in older women. J Am Geriatr Soc. 2002 May;50(5):808-16. PMID 12028165.
7. Goode PS. Behavioral and drug therapy for urinary incontinence. Urology. 2004 Mar;63(3 Suppl 1):58-64. PMID 15013654.
8. Cardozo L, Castro-Diaz D, Gittelman M, et al. Reductions in overactive bladder-related incontinence from pooled analysis of phase III trials evaluating treatment with solifenacin. Int Urogynecol J Pelvic Floor Dysfunct. 2006 Sep;17(5):512-9. PMID 16625311..
9. Chapple C, Van Kerrebroeck P, Tubaro A, et al. Clinical efficacy, safety, and tolerability of once-daily fesoterodine in subjects with overactive bladder. Eur Urol. 2007 Oct;52(4):1204-12. PMID 17651893.
10. Chapple CR, Van Kerrebroeck PE, Junemann KP, et al. Comparison of fesoterodine and tolterodine in patients with overactive bladder. BJU Int. 2008 Nov;102(9):1128-32. PMID 18647298.
11. Chapple C, DuBeau C, Ebinger U, et al. Darifenacin treatment of patients >or= 65 years with overactive bladder: results of a randomized, controlled, 12-week trial. Curr Med Res Opin. 2007 Oct;23(10):2347-58. PMID 17706004.
12. Chapple CR, Abrams P. Comparison of darifenacin and oxybutynin in patients with overactive bladder: assessment of ambulatory urodynamics and impact on salivary flow. Eur Urol. 2005 Jul;48(1):102-9. PMID 15936869.
13. Chapple C, Steers W, Norton P, et al. A pooled analysis of three phase III studies to investigate the efficacy, tolerability and safety of darifenacin, a muscarinic M3 selective receptor antagonist, in the treatment of overactive bladder. BJU Int. 2005 May;95(7):993-1001. PMID 15839920.
14. Fesoterodine a new effective and well-tolerated antimuscarinic for the treatment of urgency-frequency syndrome:results of a phase 2 controlled study. 2004 Congress of the International Continence Society; August 25-27, 2004; Paris, France. Abstract 142; 2004.
15. Chapple CR, Rechberger T, Al-Shukri S, et al. Randomized, double-blind placebo- and tolterodine-controlled trial of the once-daily antimuscarinic agent solifenacin in patients with symptomatic overactive bladder. BJU Int. 2004 Feb;93(3):303-10. PMID 14764127.
16. Chapple CR. Darifenacin: a novel M3 muscarinic selective receptor antagonist for the treatment of overactive bladder. Expert Opin Investig Drugs. 2004 Nov;13(11):1493-500. PMID 15500396.

17. Choo MS, Lee JZ, Lee JB, et al. Efficacy and safety of solifenacin succinate in Korean patients with overactive bladder: a randomised, prospective, double-blind, multicentre study. Int J Clin Pract. 2008 Nov;62(11):1675-83. PMID 19143854.

18. Chu F, Smith N, Uchida T. Efficacy and safety of solifenacin succinate 10 mg once Daily: A multicenter, phase III, randomized, double-blind, placebo-controlled, parallel-group trial in patients with overactive bladder. Current Therapeutic Research. 2009 December;70(6):405-20. PMID 10.1016/j.curtheres.2009.11.001.

19. Diokno AC, Appell RA, Sand PK, et al. Prospective, randomized, double-blind study of the efficacy and tolerability of the extended-release formulations of oxybutynin and tolterodine for overactive bladder: results of the OPERA trial. Mayo Clin Proc. 2003 Jun;78(6):687-95. PMID 12934777.

20. Armstrong RB, Luber KM, Peters KM. Comparison of dry mouth in women treated with extended-release formulations of oxybutynin or tolterodine for overactive bladder. Int Urol Nephrol. 2005;37(2):247-52. PMID 16142551.

21. Chu FM, Dmochowski RR, Lama DJ, et al. Extended-release formulations of oxybutynin and tolterodine exhibit similar central nervous system tolerability profiles: a subanalysis of data from the OPERA trial. Am J Obstet Gynecol. 2005 Jun;192(6):1849-54; discussion 54-5. PMID 15970828.

22. Anderson RU, MacDiarmid S, Kell S, et al. Effectiveness and tolerability of extended-release oxybutynin vs extended-release tolterodine in women with or without prior anticholinergic treatment for overactive bladder. Int Urogynecol J Pelvic Floor Dysfunct. 2006 Sep;17(5):502-11. PMID 16724169.

23. Dmochowski RR, Peters KM, Morrow JD, et al. Randomized, double-blind, placebo-controlled trial of flexible-dose fesoterodine in subjects with overactive bladder. Urology. 2010 Jan;75(1):62-8. PMID 19931895.

24. Dmochowski RR, Sand PK, Zinner NR, et al. Trospium 60 mg once daily (QD) for overactive bladder syndrome: results from a placebo-controlled interventional study. Urology. 2008 Mar;71(3):449-54. PMID 18342185.

25. Dorschner W, Stolzenburg JU, Griebenow R, et al. Efficacy and cardiac safety of propiverine in elderly patients - a double-blind, placebo-controlled clinical study. Eur Urol. 2000 Jun;37(6):702-8. PMID 10828671.

26. Drutz HP, Appell RA, Gleason D, et al. Clinical efficacy and safety of tolterodine compared to oxybutynin and placebo in patients with overactive bladder. Int Urogynecol J Pelvic Floor Dysfunct. 1999;10(5):283-9. PMID 10543335.

27. Halaska M, Ralph G, Wiedemann A, et al. Controlled, double-blind, multicentre clinical trial to investigate long-term tolerability and efficacy of trospium chloride in patients with detrusor instability. World J Urol. 2003 May;20(6):392-9. PMID 12811500.

28. Herschorn S, Swift S, Guan Z, et al. Comparison of fesoterodine and tolterodine extended release for the treatment of overactive bladder: a head-to-head placebo-controlled trial. BJU Int. 2010 Jan;105(1):58-66. PMID 20132103.

29. Herschorn S, Heesakkers J, Castro-Diaz D, et al. Effects of tolterodine extended release on patient perception of bladder condition and overactive bladder symptoms*. Curr Med Res Opin. 2008 Dec;24(12):3513-21. PMID 19032133.

30. Hill S, Khullar V, Wyndaele JJ, et al. Dose response with darifenacin, a novel once-daily M3 selective receptor antagonist for the treatment of overactive bladder: results of a fixed dose study. Int Urogynecol J Pelvic Floor Dysfunct. 2006 May;17(3):239-47. PMID 15999217.

31. Homma Y, Paick JS, Lee JG, et al. Clinical efficacy and tolerability of extended-release tolterodine and immediate-release oxybutynin in Japanese and Korean patients with an overactive bladder: a randomized, placebo-controlled trial. BJU Int. 2003 Nov;92(7):741-7. PMID 14616458.

32 Takei M, Homma Y. Long-term safety, tolerability and efficacy of extended-release tolterodine in the treatment of overactive bladder in Japanese patients. Int J Urol. 2005 May;12(5):456-64. PMID 15948744.

33. Homma Y, Kawabe K. Health-related quality of life of Japanese patients with overactive bladder treated with extended-release tolterodine or immediate-release oxybutynin: a randomized, placebo-controlled trial. World J Urol. 2004 Oct;22(4):251-6. PMID 15455256.

34. Jacquetin B, Wyndaele J. Tolterodine reduces the number of urge incontinence episodes in patients with an overactive bladder. Eur J Obstet Gynecol Reprod Biol. 2001 Sep;98(1):97-102. PMID 11516807.

35. Johnson TM, 2nd, Burgio KL, Redden DT, et al. Effects of behavioral and drug therapy on nocturia in older incontinent women. J Am Geriatr Soc. 2005 May;53(5):846-50. PMID 15877562.

36. Junemann KP, Al-Shukri S. Efficacy and tolerability of trospium cholride and tolterodine in 234 patients with urge syndrome: a double-bline, placebo-controlled, multicentre clinical trial. Neurourol Urodyn. 2000;19:488-90. PMID 85B.

37. Superior efficacy of fesoterodine over tolterodine with rapid onset: A prospective, head-to-head, placebo-controlled trial. Neurourology and Urodynamics; 2010; Joint Meeting of the International Continence Society and the International Urogynecological Association, Toronto, Canada, 23-27 August 2010. 29.

38. Kaplan SA, Schneider T, Foote JE, et al. Superior efficacy of fesoterodine over tolterodine extended release with rapid onset: a prospective, head-to-head, placebo-controlled trial. BJU Int. 2011 May;107(9):1432-40. PMID 20860717.

39. Karram MM, Toglia MR, Serels SR, et al. Treatment with solifenacin increases warning time and improves symptoms of overactive bladder: results from VENUS, a randomized, double-blind, placebo-controlled trial. Urology. 2009 Jan;73(1):14-8. PMID 18995887.

40. Solifenacin for overactive bladder: patient-reported outcomes from a large placebo-controlled trial. Postgrad Med. 2009 Sep;121(5):151-8. PMID 19820284.

41. Kelleher CJ, Reese PR, Pleil AM, et al. Health-related quality of life of patients receiving extended-release tolterodine for overactive bladder. The American journal of managed care; 2002. p. S608-15.

42. Zinner NR, Mattiasson A, Stanton SL. Efficacy, safety, and tolerability of extended-release once-daily tolterodine treatment for overactive bladder in older versus younger patients. J Am Geriatr Soc. 2002 May;50(5):799-807. PMID 12028164.

43. Van Kerrebroeck P, Kreder K, Jonas U, et al. Tolterodine once-daily: superior efficacy and tolerability in the treatment of the overactive bladder. Urology. 2001 Mar;57(3):414-21. PMID 11248608.

44. Dmochowski R, Kreder K, MacDiarmid S, et al. The clinical efficacy of tolterodine extended-release is maintained for 24 h in patients with overactive bladder. BJU Int. 2007 Jul;100(1):107-10. PMID 17552957.

45. Wein AJ, Khullar V, Wang JT, et al. Achieving continence with antimuscarinic therapy for overactive bladder: effects of baseline incontinence severity and bladder diary duration. BJU Int. 2007 Feb;99(2):360-3. PMID 17155987.

46. Landis JR, Kaplan S, Swift S, et al. Efficacy of antimuscarinic therapy for overactive bladder with varying degrees of incontinence severity. J Urol. 2004 Feb;171(2 Pt 1):752-6. PMID 14713803.

47. Swift S, Garely A, Dimpfl T, et al. A new once-daily formulation of tolterodine provides superior efficacy and is well tolerated in women with overactive bladder. Int Urogynecol J Pelvic Floor Dysfunct. 2003 Feb;14(1):50-4; discussion 4-5. PMID 12601517.

48. Freeman R, Hill S, Millard R, et al. Reduced perception of urgency in treatment of overactive bladder with extended-release tolterodine. Obstet Gynecol. 2003 Sep;102(3):605-11. PMID 12962951.

49. Khullar V, Hill S, Laval KU, et al. Treatment of urge-predominant mixed urinary incontinence with tolterodine extended release: a randomized, placebo-controlled trial. Urology. 2004 Aug;64(2):269-74; discussion 74-5. PMID 15302476.

50. DuBeau CE, Khullar V, Versi E. "Unblinding" in randomized controlled drug trials for urinary incontinence: Implications for assessing outcomes when adverse effects are evident. Neurourol Urodyn. 2005;24(1):13-20. PMID 15570576.

51. Lee KS, Lee HW, Choo MS, et al. Urinary urgency outcomes after propiverine treatment for an overactive bladder: the 'Propiverine study on overactive bladder including urgency data'. BJU Int. 2010 Jun;105(11):1565-70. PMID 19912183.

52. Lee JG, Hong JY, Choo MS, et al. Tolterodine: as effective but better tolerated than oxybutynin in Asian patients with symptoms of overactive bladder. Int J Urol. 2002 May;9(5):247-52. PMID 12060436.

53. Lehtoranta K, Tainio H, Lukkari-Lax E, et al. Pharmacokinetics, efficacy, and safety of intravesical formulation of oxybutynin in patients with detrusor overactivity. Scand J Urol Nephrol. 2002 Feb;36(1):18-24. PMID 12002352.

54. Madersbacher H, Halaska M, Voigt R, et al. A placebo-controlled, multicentre study comparing the tolerability and efficacy of propiverine and oxybutynin in patients with urgency and urge incontinence. BJU Int. 1999 Oct;84(6):646-51. PMID 10510109.

55. Malone-Lee JG, Al-Buheissi S. Does urodynamic verification of overactive bladder determine treatment success? Results from a randomized placebo-controlled study. BJU Int. 2009 Apr;103(7):931-7. PMID 19281469.

56. Malone-Lee JG, Walsh JB, Maugourd MF. Tolterodine: a safe and effective treatment for older patients with overactive bladder. J Am Geriatr Soc. 2001 Jun;49(6):700-5. PMID 11454106.

57. Moore KH, Hay DM, Imrie AE, et al. Oxybutynin hydrochloride (3 mg) in the treatment of women with idiopathic detrusor instability. Br J Urol. 1990 Nov;66(5):479-85. PMID 2249115.

58. NCT00444925. Clinical Trial to Evaluate the Efficacy and Safety of Fesoterodine in Comparison to Tolterodine for Overactive Bladder (OAB). http://www.clinicaltrials.gov/ct2/show/NCT00444925?term=NCT00444925&rank=1.

59. Rentzhog L, Stanton SL, Cardozo L, et al. Efficacy and safety of tolterodine in patients with detrusor instability: a dose-ranging study. Br J Urol. 1998 Jan;81(1):42-8. PMID 9467475.

60. Rogers RG, Bachmann G, Scarpero H, et al. Effects of tolterodine ER on patient-reported outcomes in sexually active women with overactive bladder and urgency urinary incontinence. Curr Med Res Opin. 2009 Sep;25(9):2159-65. PMID 19601704.

61. Rogers R, Bachmann G, Jumadilova Z, et al. Efficacy of tolterodine on overactive bladder symptoms and sexual and emotional quality of life in sexually active women. Int Urogynecol J Pelvic Floor Dysfunct. 2008 Nov;19(11):1551-7. PMID 18685795.

62. Rogers RG, Omotosho T, Bachmann G, et al. Continued symptom improvement in sexually active women with overactive bladder and urgency urinary incontinence treated with tolterodine ER for 6 months. Int Urogynecol J Pelvic Floor Dysfunct. 2009 Apr;20(4):381-5. PMID 19132285.

63. Rudy D, Cline K, Harris R, et al. Time to onset of improvement in symptoms of overactive bladder using antimuscarinic treatment. BJU Int. 2006 Mar;97(3):540-6. PMID 16469022.

64. Sand PK, Morrow JD, Bavendam T, et al. Efficacy and tolerability of fesoterodine in women with overactive bladder. Int Urogynecol J Pelvic Floor Dysfunct. 2009 Jul;20(7):827-35. PMID 19495545.

65. Nitti C VW, Dmochowski R, Sand PK, et al. Efficacy, safety and tolerability of fesoterodine for overactive bladder syndrome. J Urol. 2007 Dec;178(6):2488-94. PMID 17937959.

66. Sand PK, Dmochowski RR, Zinner NR, et al. Trospium chloride extended release is effective and well tolerated in women with overactive bladder syndrome. Int Urogynecol J Pelvic Floor Dysfunct. 2009 Aug 29. PMID 19727537.

67. Dmochowski RR, Rosenberg MT, Zinner NR, et al. Extended-release trospium chloride improves quality of life in overactive bladder. Value Health. 2010 Mar;13(2):251-7. PMID 19818062.

68. Staskin DR, Te AE. Short- and long-term efficacy of solifenacin treatment in patients with symptoms of mixed urinary incontinence. BJU Int. 2006 Jun;97(6):1256-61. PMID 16686722.

69. Staskin D, Sand P, Zinner N, et al. Once daily trospium chloride is effective and well tolerated for the treatment of overactive bladder: results from a multicenter phase III trial. J Urol. 2007 Sep;178(3 Pt 1):978-83; discussion 83-4. PMID 17632131.

70. Staskin DR, Harnett MD. Effect of trospium chloride on somnolence and sleepiness in patients with overactive bladder. Curr Urol Rep. 2004 Dec;5(6):423-6. PMID 15541209.

71. Staskin DR, Dmochowski RR, Sand PK, et al. Efficacy and safety of oxybutynin chloride topical gel for overactive bladder: a randomized, double-blind, placebo controlled, multicenter study. J Urol. 2009 Apr;181(4):1764-72. PMID 19233423.

72. Steers W, Corcos J, Foote J, et al. An investigation of dose titration with darifenacin, an M3-selective receptor antagonist. BJU Int. 2005 Mar;95(4):580-6. PMID 15705084.

73. Szonyi G, Collas DM, Ding YY, et al. Oxybutynin with bladder retraining for detrusor instability in elderly people: a randomized controlled trial. Age Ageing. 1995/07/01 ed; 1995. p. 287-91.

74. Thuroff JW, Bunke B, Ebner A, et al. Randomized, double-blind, multicenter trial on treatment of frequency, urgency and incontinence related to detrusor hyperactivity: oxybutynin versus propantheline versus placebo. J Urol. 1991 Apr;145(4):813-6; discussion 6-7. PMID 2005707.

75. Toglia MR, Ostergard DR, Appell RA, et al. Solifenacin for overactive bladder: secondary analysis of data from VENUS based on baseline continence status. Int Urogynecol J Pelvic Floor Dysfunct. 2010 Jul;21(7):847-54. PMID 20339833.

76. U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Solifenacin in the treatment of urgency symptoms of overactive bladder in a rising dose, randomized, placebo-controlled, double-blind trial (SUNRISE). www.clinicalstudyresults.org/documents/company-study_8351_0.pdf. Accessed on June 25 2010.

77. Cardozo L, Hessdorfer E, Milani R, et al. Solifenacin in the treatment of urgency and other symptoms of overactive bladder: results from a randomized, double-blind, placebo-controlled, rising-dose trial. BJU Int. 2008 Nov;102(9):1120-7. PMID 18990175.

78. U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Medical Review for Enablex (Clarifenacin) Extended Release Tablets. 2004. www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-513_Enablex.cfm. Accessed on June 25 2010.

79. U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Statistical Review for Enablex (Darifenacin Hydrobromide) Extended Release Tablets. 2004. www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-513_Enablex.cfm. Accessed on June 25 2010.

80. U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Medical Review for Sanctura XR (Trospium Chloride) Extended Release Capsules. 2007. www.accessdata.fda.gov/drugsatfda_docs/nda/2007/022103s000TOC.cfm. Accessed June 25 2010.

81. U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Statistical Review for Sanctura XR (Trospium Chloride) Extended Release Capsules. 2007. www.accessdata.fda.gov/drugsatfda_docs/nda/2007/022103s000TOC.cfm. Accessed on June 25 2010.

82. Chapple CR, Martinez-Garcia R, Selvaggi L, et al. A comparison of the efficacy and tolerability of solifenacin succinate and extended release tolterodine at treating overactive bladder syndrome: results of the STAR trial. Eur Urol. 2005 Sep;48(3):464-70. PMID 15990220.

83. Chapple CR, Fianu-Jonsson A, Indig M, et al. Treatment outcomes in the STAR study: a subanalysis of solifenacin 5 mg and tolterodine ER 4 mg. Eur Urol. 2007 Oct;52(4):1195-203. PMID 17574730.

84. Pharmaceutical Research and Manufacturers of America. Solifenacin in a flexible dose regimen with tolterodine as an active comparator in a double-blind, double-dummy, randomized overactive bladder symptom trial (STAR). www.clinicalstudyresults.org/documents/company-study_8350_0.pdf. Accessed June 25 2010.

85. Vardy MD, Mitcheson HD, Samuels TA, et al. Effects of solifenacin on overactive bladder symptoms, symptom bother and other patient-reported outcomes: results from VIBRANT - a double-blind, placebo-controlled trial. Int J Clin Pract. 2009 Dec;63(12):1702-14. PMID 19930331.

86. Wang AC, Chih SY, Chen MC. Comparison of electric stimulation and oxybutynin chloride in management of overactive bladder with special reference to urinary urgency: a randomized placebo-controlled trial. Urology. 2006 Nov;68(5):999-1004. PMID 17113893.

87. Yamaguchi O, Marui E, Kakizaki H, et al. Randomized, double-blind, placebo- and propiverine-controlled trial of the once-daily antimuscarinic agent solifenacin in Japanese patients with overactive bladder. BJU Int. 2007 Sep;100(3):579-87. PMID 17669143.

88. Zellner M, Madersbacher H, Palmtag H, et al. Trospium chloride and oxybutynin hydrochloride in a german study of adults with urinary urge incontinence: results of a 12-week, multicenter, randomized, double-blind, parallel-group, flexible-dose noninferiority trial. Clin Ther. 2009 Nov;31(11):2519-39. PMID 20109997.

89. Bodeker RH, Madersbacher H, Neumeister C, et al. Dose escalation improves therapeutic outcome: post hoc analysis of data from a 12-week, multicentre, double-blind, parallel-group trial of trospium chloride in patients with urinary urge incontinence. BMC Urol. 2010;10:15. PMID 20840754.

90. Zinner N, Tuttle J, Marks L. Efficacy and tolerability of darifenacin, a muscarinic M3 selective receptor antagonist (M3 SRA), compared with oxybutynin in the treatment of patients with overactive bladder. World J Urol. 2005 Sep;23(4):248-52. PMID 16096831.

91. Zinner N, Susset J, Gittelman M, et al. Efficacy, tolerability and safety of darifenacin, an M(3) selective receptor antagonist: an investigation of warning time in patients with OAB. Int J Clin Pract. 2006 Jan;60(1):119-26. PMID 16409440.

92. Zinner N, Gittelman M, Harris R, et al. Trospium chloride improves overactive bladder symptoms: a multicenter phase III trial. J Urol. 2004 Jun;171(6 Pt 1):2311-5, quiz 435. PMID 15126811.