The Efficacy and Safety of Combined Therapy with α-Blockers and Anticholinergics for Men with Benign Prostatic Hyperplasia: A Meta-Analysis

Christopher P. Filson,* John M. Hollingsworth,* J. Quentin Clemens† and John T. Wei*,‡

From the Division of Health Services Research (CPF, JMH, JQC, JTW) and Division of Neurourology and Pelvic Reconstructive Surgery, Department of Urology (JQC), University of Michigan Medical School, Ann Arbor, Michigan

Purpose: We performed a meta-analysis to compare treatment with α-blockers and anticholinergics (ie combination therapy) to α-blocker monotherapy to clarify the efficacy and safety of this treatment approach among men with storage urinary symptoms related to benign prostatic hyperplasia.

Materials and Methods: We searched for trials of men with benign prostatic hyperplasia/lower urinary tract symptoms that were randomized to combination treatment or α-blockers alone. We pooled data from 7 placebo controlled trials meeting inclusion criteria. Primary outcomes of interest included changes in International Prostate Symptom Score (storage subscores) and urinary frequency. We also assessed post-void residual volume, maximal flow rate and the incidence of urinary retention. Data were pooled using random effects models for continuous outcomes and the Peto method to generate odds ratios for acute urinary retention.

Results: Combination therapy had a significantly greater reduction in International Prostate Symptom Score storage subscores (Δ −0.73, 95% CI −1.09 − −0.37) and voiding frequency (Δ −0.69 voids, 95% CI −0.97 − −0.41). There was also a greater reduction in maximal urinary flow rate (Δ −0.59 ml per second, 95% CI −1.04 − −0.14) and increase in post-void residual urine volume (Δ 11.60 ml, 95% CI 8.50−14.70) with combination therapy. The number needed to treat with combination therapy to cause 1 acute urinary retention episode was 101 (95% CI 60−267).

Conclusions: Combination treatment with α-blockers and anticholinergics significantly improved storage voiding parameters compared to men treated with α-blocker therapy alone. This treatment approach is safe with a minimal risk of increased post-void residual urine volume, decreased maximal urinary flow rate or acute urinary retention.

Abbreviations and Acronyms

AUR = acute urinary retention

BPH = benign prostatic hyperplasia

CO = combination therapy

ER = extended release

I-PSS = International Prostate Symptom Score

LUTS = lower urinary tract symptoms

PVR = post-void residual urine volume

Qmax = maximal urinary flow rate

RCT = randomized clinical trial

WMD = weighted mean difference

Accepted for publication May 23, 2013.

Supported by the National Institutes of Health Training in Clinical Investigation in Urology grant (NIH-T32-DK007782).

* Nothing to disclose.

† Financial interest and/or other relationship with Medtronic, Afferent Pharmaceuticals, Amphora Medical, Endo Pharmaceuticals and Allergan.

‡ Correspondence: Dow Division of Health Services Research, Department of Urology, University of Michigan, 2800 Plymouth Rd., Building 16, 1st Floor, Ann Arbor, Michigan 48109; (e-mail: jtwei@med.umich.edu).

See Editorial on page 1976.

Editor's Note: This article is the fourth of 5 published in this issue for which category 1 CME credits can be earned. Instructions for obtaining credits are given with the questions on pages 2316 and 2317.

0022-5347/13/1906-2153/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2013.05.058
Vol. 190, 2153-2160, December 2013
Printed in U.S.A.

Key Words: prostatic hyperplasia, cholinergic antagonists, adrenergic alpha-antagonists, combined modality therapy, meta-analysis

To date, established medical interventions for men with LUTS associated with benign prostatic hyperplasia/enlargement (eg α-blockers and 5α-reductase inhibitors) have focused on the obstructive aspect of patients' symptoms. However, more than 40% of men have a significant storage component to their symptoms and 16% exhibit symptoms of an overactive bladder.[1,2] This suggests that anticholinergics may have a role in symptom amelioration in certain men with BPH/LUTS.

Indeed, prior randomized controlled trials have demonstrated the efficacy of combination therapy with α-blockers and anticholinergics.[3,4] However, existing trials report a variety of outcomes with inconsistent findings. Furthermore, population based data suggest that anticholinergic therapy is rarely used to treat men with BPH, with less than 3% of receiving anticholinergics.[5] This infrequent use is widely held to be driven by fears of exacerbation of obstructive symptoms and urinary retention in an elderly population with BPH.

To better define the efficacy and safety of this treatment approach, we performed a meta-analysis of randomized clinical trials to quantify the effects of combination therapy (ie anticholinergic medication in addition to an α-blocker) compared to α-blocker monotherapy.

MATERIALS AND METHODS

Eligibility Criteria

Following the guidelines from the Quality of Reporting of Meta-Analyses conference,[6] we established inclusion criteria before our search. We planned to include only placebo controlled, RCTs of men with BPH that compared combination therapy to α-blocker monotherapy. We excluded studies examining medical therapy for men who were treated with surgery for BPH. We excluded observational studies without a control group, those evaluating anticholinergic monotherapy and trials where the control group only received placebo.

Search Strategy

We searched MEDLINE®, Pre-MEDLINE, the Cochrane Register of Controlled Trials, EMBASE and ClinicalTrials.gov databases for trials of interest. We considered all publications in any language published before September 12, 2012. Our search strategy combined and exploded terms for "benign prostatic hyperplasia," "bladder outlet obstruction," "anticholinergics" and "antimuscarinics". We also included specific generic and trade drug names in our search. We contacted major drug companies regarding recently completed trials for which data were available. We reviewed the references of selected randomized trials to identify other publications potentially missed by our initial search.

Study Selection

Quality of the randomized trials was assessed based on method of randomization, allocation concealment, blinding, evidence of selective reporting, rates of completion of assigned intervention and the group used for final statistical analysis (ie full analysis set vs intent to treat).[7] We included studies that were deemed high quality by consensus between study authors.

Outcomes of Interest and Data Extraction

The primary outcomes of interest were changes in the I-PSS storage subscores and urinary frequency, which both reflect storage LUTS among men with BPH.[8] Secondary outcomes of interest included Qmax, PVR and the incidence of AUR. Data were abstracted using a standardized form and inconsistencies with data were discussed until consensus was reached with study authors. We attempted to contact study authors to clarify questions on study design or to supplement missing data from individual publications.

Statistical Analysis

For continuous outcomes, the effect size of interest was the difference in pre-intervention and post-intervention mean scores or values (ie weighted mean difference). One trial with 2 intervention arms with varied doses had the respective means and standard deviations pooled for comparison to the control group.[9] Missing standard deviations for pretreatment and posttreatment mean values were imputed by using the arithmetic mean of available standard deviations.[10] Missing standard deviations for change scores were calculated using pre-intervention and post-intervention means and standard deviations, with a correlation coefficient of 0.5.[11] Due to clinical differences between RCTs (ie medication types, inclusion criteria) we pooled WMDs using DerSimonian and Laird random effects models.[12] As AUR and urethral catheterization were rare events, we used the Peto method of calculating odds ratios for both of these dichotomous outcomes.[13]

Statistical heterogeneity was assessed with the I^2 statistic, which measures the proportion of inconsistency in individual studies not explained by chance.[14] To assess for publication bias, funnel plots were created for each outcome and qualitatively assessed. Influence analyses assessed whether significant findings were affected by exclusion of individual trials. Sensitivity analyses were carried out with variations of the correlation coefficient (ie $r = 0.0$, 0.25 and 0.80). Subgroup analyses were planned a priori and performed to try to understand statistical heterogeneity between trials. As prior exposure to α-blockers may influence treatment effect, we stratified our forest plots based on this variable. All tests were

2-tailed and we set the probability of Type 1 error at 0.05. Stata® version 11.0 was used for all statistics.

RESULTS

A total of 2,198 references were identified in the initial database search (fig. 1). Through an abstract review we excluded all references related to other topics, nonhuman studies, editorials, alternate study designs (ie observational studies) and duplicate references. Fifty potentially relevant RCTs were evaluated more closely with a review of the full text and 43 articles were then excluded resulting in a total of 7 RCTs which met study criteria.

In total, 3,629 patients were randomized in the 7 pooled studies (see table). Different types of anticholinergic medications were evaluated, including tolterodine,[4,15,16] oxybutynin ER,[17] solifenacin,[9,18] and fesoterodine.[19] Five trials allowed use of α-blockers before trial entry (ie add-on therapy).[9,16–19] Four trials evaluated tamsulosin as the α-blocker,[4,9,17,18] 2 trials did not specify α-blocker type,[16,19] and the remaining trial included doxazosin.[15] Only 1 trial had a true intent to treat analysis where all randomized patients were included in the final analysis.[15] The remaining trials analyzed only the patients who had taken at least 1 dose of their assigned medication (ie full analysis set). However, all trials had less than 7% of randomized patients excluded from the final efficacy analyses (see table). All trials had blinded allocation to both

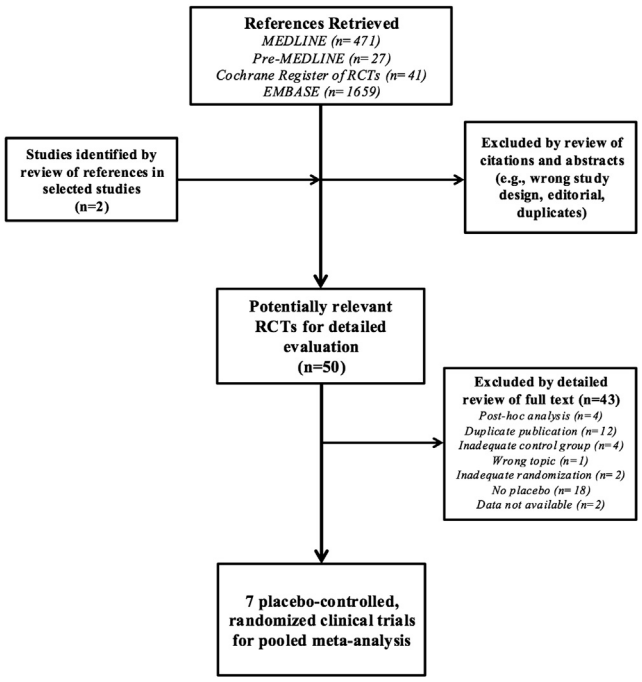

Figure 1. Study selection process for trials included in meta-analysis.

Characteristics of included randomized clinical trials

References	α-blocker (No. randomized)	Anticholinergic (No. randomized)	Primary Outcome	No./Total No. Randomized but Excluded from Analysis (%)	Prior α-Blocker	Type of Analysis	Inclusion Criteria				Exclusion Criteria
							I-PSS	*I-PSS (storage)*	*Frequency (episodes/24 hrs)*	*Urgency (episodes/24 hrs)*	*PVR (ml)*
Kaplan et al.[4]	Tamsulosin 0.4 mg daily (215)	Tolterodine ER 4 mg daily (225)	Perception of benefit	14/440 (3)	No	Intent to treat*	12 or Greater	—	8 or Greater	2 or Greater	200 or Less
MacDiarmid et al.[17]	Tamsulosin 0.4 mg daily (210)	Oxybutynin ER 10 mg daily (210)	Change in I-PSS	11/420 (3)	Yes	Full analysis set	13 or Greater	8 or Greater	—	—	150 or Less
Chapple et al.[16]	Various (323)	Tolterodine ER 4 mg daily (329)	Perception of benefit	42/652 (6)	Yes	Full analysis set	—	—	8 or Greater	2 or Greater	200 or Less
Kaplan et al.[18]	Tamsulosin 0.4 mg daily (195)	Solifenacin 5 mg daily (203)	Voiding frequency	26/398 (7)	Yes	Full analysis set	13 or Greater	—	8 or Greater	1 or Greater	200 or Less
Kaplan et al.[19]	Various (473)	Fesoterodine 4-8 mg daily (474)	Voiding urgency	4/947 (less than 1)	Yes	Full analysis set	—	—	8 or Greater	1 or Greater	200 or Less
Lee et al.[15]	Doxazosin 4 mg daily (91)	Tolterodine ER 4 mg daily (85)	Change in I-PSS (storage)	0/176 (0)	No	Intent to treat	14 or Greater	6 or Greater	8 or Greater	1 or Greater	—
Yamaguchi et al.[9]	Tamsulosin 0.2 mg daily (215)	Solifenacin 2.5-5.0 mg daily (423)	Voiding urgency	2/637 (less than 1)	Yes	Full analysis set	—	—	8 or Greater	2 or Greater	50 or Less

*Described as intent to treat, but 14 patients were excluded from final analysis.

patients and providers. Mean subject age ranged from 61.0 to 70.0 years (supplementary table, http://jurology.com/). Baseline I-PSS and storage scores ranged from 13.4 to 22.2 points and 7.1 to 10.3 points, respectively. Baseline PVR and Qmax values ranged from 17.8 to 60.6 ml and 10.8 to 15.7 ml per second, respectively. All of the included trials assessed endpoints after 12 weeks of therapy.

Efficacy (I-PSS storage subscores and urinary frequency)

Five individual studies demonstrated a significantly greater reduction of I-PSS storage scores with treatment with anticholinergics and α-blockers.[4,9,15–17] Combination therapy resulted in a greater reduction of I-PSS storage subscores. (WMD −0.73, 95% CI −1.09 − −0.37, p <0.01, $I^2 = 83.5\%$). This effect was significant irrespective of prior exposure to α-blockers, with a greater effect seen with prior α-blocker use (WMD −1.07, 95% CI −1.75 − −0.38, p <0.01, $I^2 = 87.1\%$, fig. 2, *A*).

Of the 6 studies with available data, 5 showed a greater reduction in urinary frequency with combination therapy.[4,9,15,16,19] Each study reporting this outcome used patient bladder diaries for documentation. Patients treated with combination therapy

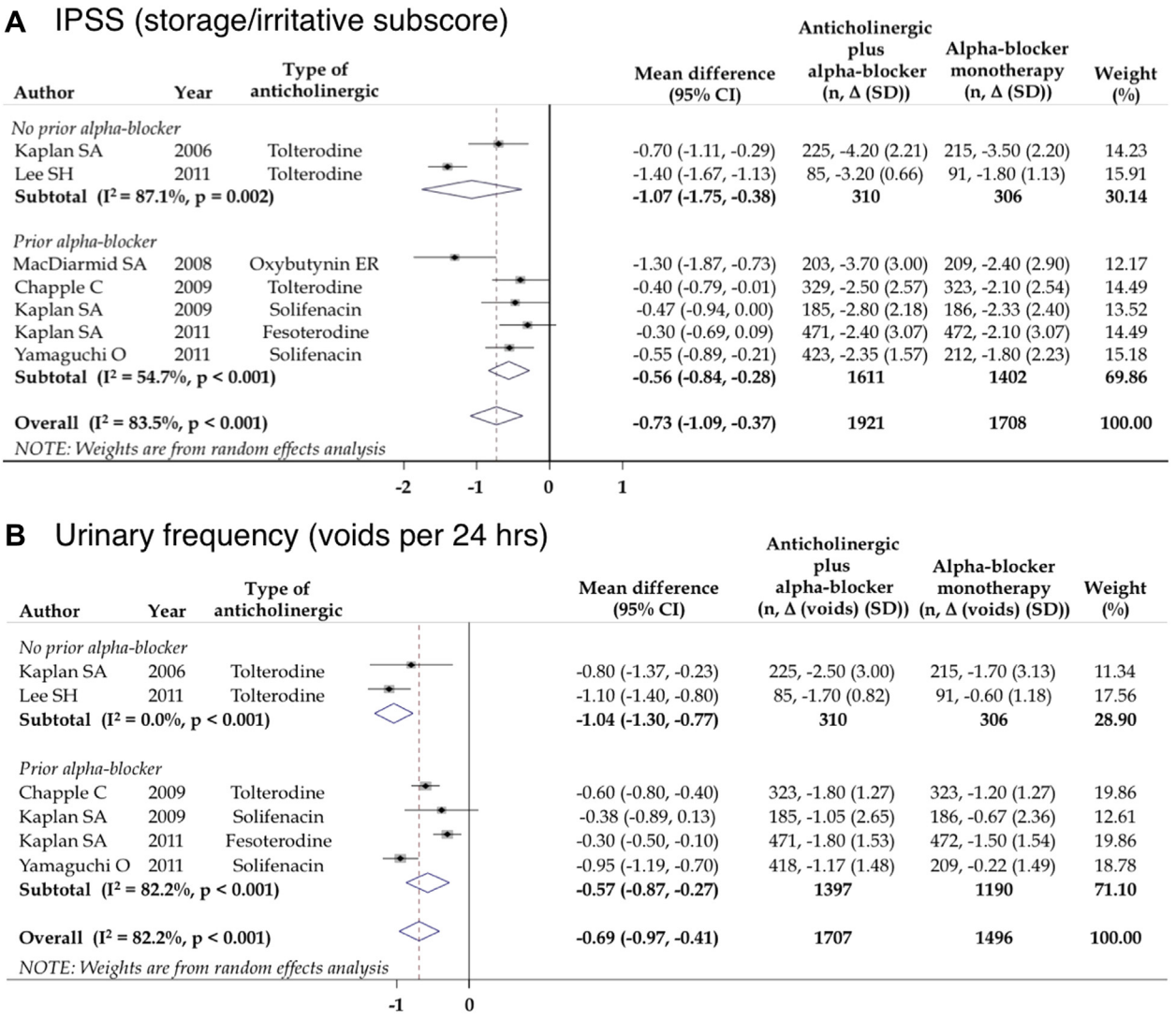

Figure 2. Forest plots of primary outcomes from pooled analysis, stratified by prior use of α-blockers. Figure is divided between 2 primary outcomes of interest for meta-analysis. Mean difference is difference between treatment effect of combination therapy compared to α-blocker monotherapy. Sizes of data markers are proportional to weight of each study in analysis. Horizontal bars represent 95% CI for each study. X axis represents magnitude of change of each outcome of interest. Data to left of black vertical line represent greater reduction of each outcome with combination therapy and data to right represent greater increase with combination therapy. White diamonds represent pooled effect sizes for each subgroup and overall, which extend to 95% CI of pooled data. Gray broken vertical line represents value of overall pooled effect size. P values correspond to test of significance for pooled data. I^2 values represent heterogeneity of each analysis.

had fewer voids per 24 hours compared to those treated with α-blockers alone (WMD −0.69 voids per 24 hours, 95% CI −0.97 − −0.41, p <0.01, $I^2 = 82.2\%$). There was a greater magnitude of effect among patients who had not been treated with α-blockers previously (WMD −1.04 voids per 24 hours, 95% CI −1.30 − −0.77, $I^2 = 0.0\%$, fig. 2, *B*).

Safety (Qmax, PVR and AUR)

Combination therapy increased PVR more than α-blocker monotherapy (WMD 11.60 ml, 95% CI 8.50−14.70, p <0.01, $I^2 = 0.0\%$, fig. 3, *A*). Although the finding was only significant in one individual study,[16] the pooled data showed a significantly greater reduction of Qmax with combination therapy compared to α-blocker monotherapy (WMD −0.59 ml per second, 95% CI −1.04 − −0.14, p = 0.01, $I^2 = 0.0\%$). However, there was not a statistically significant difference among studies without prior α-blocker treatment (WMD −0.41 ml per second, 95% CI −2.04−1.22, p = 0.62, fig. 3, *B*). All included studies used uroflowmetry and ultrasonography to measure Qmax and PVR, respectively.

Acute urinary retention was rare overall; only 1.4% (2 of 2,917) of patients treated with an anticholinergic and α-blocker experienced AUR,

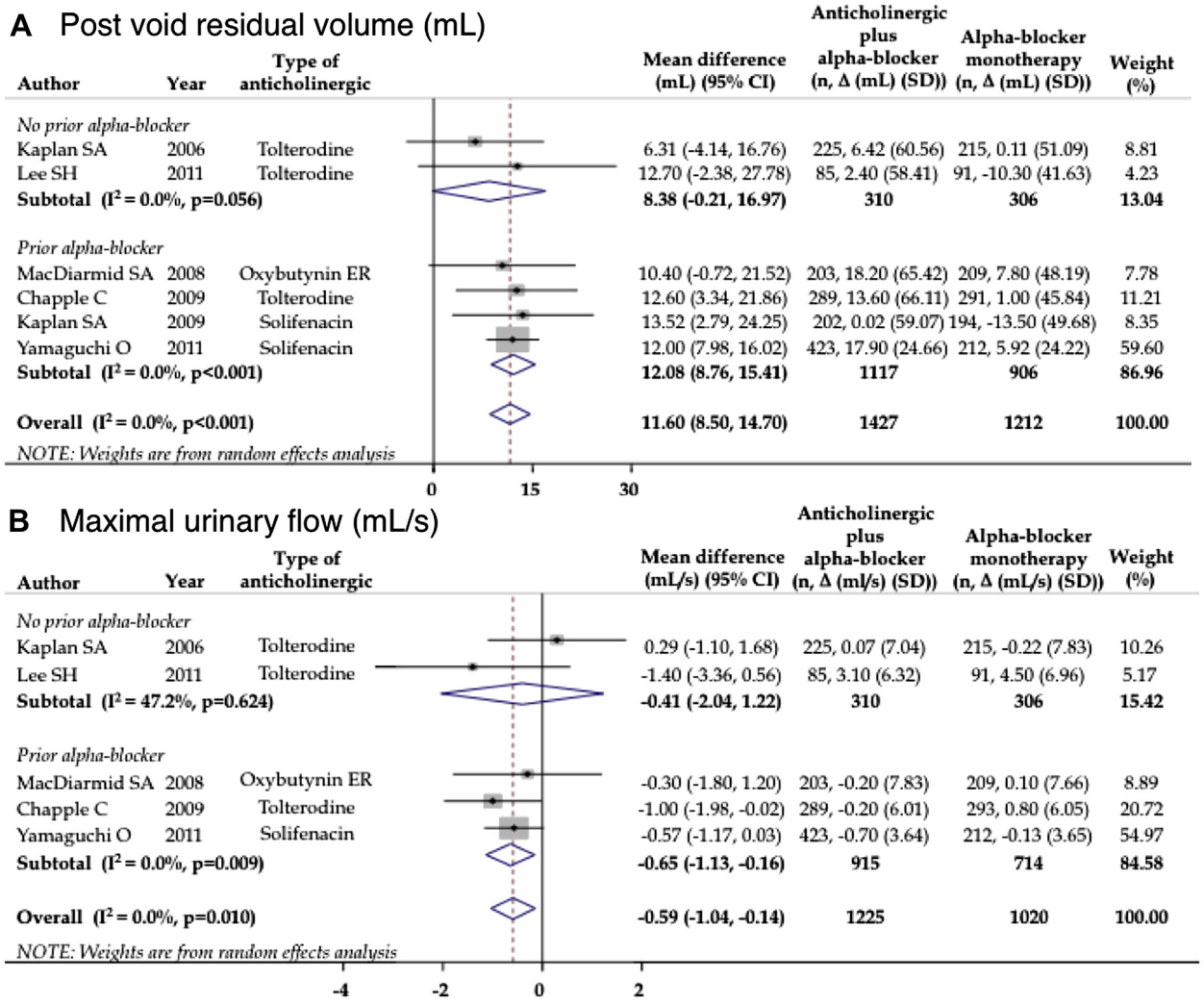

Figure 3. Forest plots of PVR and Qmax outcomes, stratified by prior use of α-blockers, divided between 2 secondary outcomes of interest for meta-analysis. Mean difference is difference between treatment effect of combination therapy compared to α-blocker monotherapy. Sizes of data markers are proportional to weight of each study in analysis. Horizontal bars represent 95% CI for each study. X axis represents magnitude of change of each outcome of interest. Data to left of black vertical line represent greater reduction of each outcome with combination therapy and data to right represent greater increase with combination therapy. White diamonds represent pooled effect sizes for each subgroup and overall, which extend to 95% CI of pooled data. Gray broken vertical line represents value of overall pooled effect size. P values correspond to test of significance for pooled data. I^2 values represent heterogeneity of each analysis.

compared to only 0.4% (7 of 1,704) on α-blocker monotherapy. Of note, only 2 trials mentioned how AUR was defined.[9,19] Although this did represent a significant increase in the odds of AUR (OR 3.05, 95% CI 1.54–6.02, $I^2 = 0.0\%$), the absolute risk increase was only 1.0%. Therefore, the number needed to treat with combination therapy to result in 1 additional case of AUR was 101 (95% CI 60–267). The requirement for urethral catheterization was exceedingly rare (0.5% with combination therapy vs 0.3% with α-blocker monotherapy) and combination therapy did not increase the odds of this complication (OR 2.44, 95% CI 0.81 − 7.39, $I^2 = 0.0\%$, fig. 4).

Results from subgroup analyses did not demonstrate any instances where the direction of effect changed significantly. The only trial that used doxazosin as an α-blocker had the greatest reduction in I-PSS storage subscores.[15] Trials that had a minimum cutoff for I-PSS storage subscores as an inclusion criterion had a greater magnitude of reduction of I-PSS storage subscores (−1.38 vs −0.49) and 24-hour voids (−1.10 vs −0.60, data available upon request). Furthermore, by our qualitative review, funnel plots assessing publication bias were distributed symmetrically and evenly for all outcomes (figures available upon request). Our influence analyses showed no significant changes

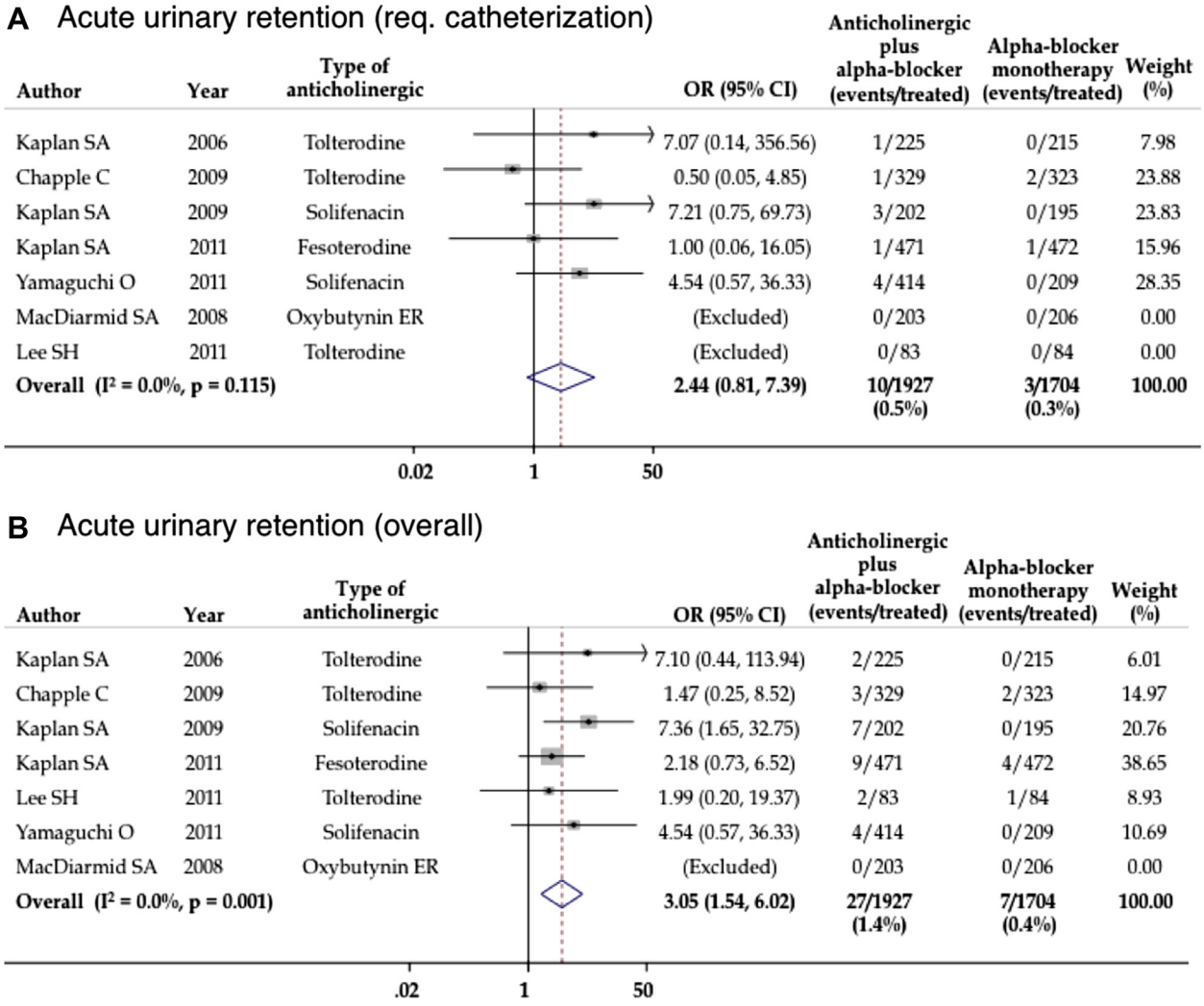

Figure 4. Forest plots of odds ratios for acute urinary retention and urethral catheterization, divided between 2 outcomes related to AUR in meta-analysis. Mean difference is difference between treatment effect of combination therapy compared to α-blocker monotherapy. Sizes of data markers are proportional to weight of each study in analysis. Horizontal bars represent 95% CI for each study. X axis represents magnitude of change of each outcome of interest. Data to left of black vertical line represent decreased odds of each outcome with combination therapy and data to right represent increased odds of each outcome with combination therapy. White diamonds represent pooled odds ratios, which extend to 95% CI of pooled data. Gray vertical line represents value of overall pooled odds ratios. P values correspond to test of significance for pooled data. I^2 values represent heterogeneity of each analysis.

regarding efficacy. Regarding safety, excluding the trial by Chapple et al[16] and the trial reported by Yamaguchi et al[9] both resulted in a marginal loss of significance for changes in Qmax (figures available upon request).

DISCUSSION

Numerous clinical trials have examined the efficacy and safety of anticholinergics combined with α-blockers for men with benign prostatic hyperplasia. However, individual trials have focused on a diverse array of primary outcomes and may have been underpowered to find significant differences in their secondary outcomes. For instance, the 7 pooled trials in this meta-analysis used 5 different primary outcomes including effects on patient perception of treatment benefit,[4] I-PSS,[17] I-PSS storage subscores,[15] urinary frequency[18] and urinary urgency.[9,19] The performance of a meta-analysis allows one to overcome this limitation by increasing statistical power with pooled data, as has been seen with medical expulsive therapy for ureteral calculi[20] and perioperative intravesical chemotherapy to minimize tumor recurrence for bladder cancer patients.[21] Since most trials presented a mixture of primary outcomes (with varied results), our meta-analysis represents a unique, cohesive presentation of the efficacy and safety associated with combination therapy for men with BPH. Although our findings parallel what has previously been described in other systematic reviews,[22] the only meta-analysis to date only quantified changes in PVR, Qmax and urodynamic parameters.[23] Furthermore, it predates the majority of the RCTs that we have incorporated into our meta-analysis.

Perhaps the most consequential finding of our meta-analysis is that the use of combination therapy among men with BPH did not have a clinically significant impact on important safety parameters (ie PVR and maximal urinary flow). Furthermore, the incidence of AUR was exceedingly rare with combination therapy, requiring treatment of over 100 individuals with anticholinergics and α-blockers to result in a single additional case of AUR. What is more, our analysis demonstrated that, compared to α-blocker monotherapy, combination therapy demonstrated significantly more improvement in clinical parameters specific to storage symptoms for men with BPH/LUTS (ie I-PSS storage subscores and urinary frequency).

Though statistically significant, we admit that these findings are of unknown clinical significance. The established change in I-PSS (overall) for men with BPH that is considered clinically significant is 4 or more points.[24] However, the findings of this study were validated among a heterogeneous BPH population, so they are not necessarily generalizable to a population with more storage LUTS. Since our meta-analysis focused on men with storage LUTS, one can speculate that clinical effects of anticholinergics among typical men with BPH (without storage symptoms) may be less impressive. Nevertheless, our study supports the notion that combination therapy with anticholinergics and α-blockers is a safe treatment modality with marginal effects on PVR, maximal urinary flow and the risk of acute urinary retention. In that context, it is also important to remember that the significant benefit of combination therapy (as opposed to α-blocker monotherapy) exists on a spectrum, with certain patients (particularly those with more storage symptoms) being more likely to show a clinically significant response.

To that end, further studies are required to address unanswered issues related to management of men with BPH with combination therapy. More work will be required to identify the group of men with BPH that would benefit most from anticholinergic therapy. Our study suggests (as expected) that men with storage related symptoms have a greater improvement in I-PSS storage subscores and voiding frequency with combination therapy. As novel anticholinergic medications emerge, future clinical trials perhaps should continue to focus on this patient population. In addition, it is unclear how anticholinergics combined with other BPH related medications (ie 5α-reductase inhibitors, phosphodiesterase-5 inhibitors) would affect storage related LUTS for men with BPH. Finally, the durability of this treatment approach is unclear, as all of the included studies only tracked patients for 3 months.

Several limitations of our analysis should be considered. We noted statistical heterogeneity in some of our analyses, but this was partially rectified by using a random effects model.[12] We included trials with different medication types and other differences in clinical characteristics. However, subgroup analyses did not find any significant differences in our results based on these factors (eg type of anticholinergic). We decided to exclude trials that did not use a placebo for the control arm, as they would be susceptible to inadequate blinding. Though this abandons available data, inclusion of such studies would likely muddy the waters and stray from the true clinical effects of combination therapy. Finally, some analyses depended on imputed or extrapolated data using validated statistical techniques. We addressed this with sensitivity analyses that changed the correlation coefficient, which did not result in any significant variation in our overall findings.

CONCLUSIONS

Combination therapy with anticholinergics and α-blockers has a significantly greater reduction in I-PSS storage scores and urinary frequency, compared to α-blockers alone. The risk of urinary retention associated with combination therapy was minimal. Combination therapy may be a reasonable option for men with BPH and LUTS, particularly if their symptoms have a significant storage component.

REFERENCES

1. Kaplan SA, Roehrborn CG, Chapple CR et al: Implications of recent epidemiology studies for the clinical management of lower urinary tract symptoms. BJU Int 2009; **103:** 48.
2. Milsom I, Abrams P, Cardozo L et al: How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. BJU Int 2001; **87:** 760.
3. Athanasopoulos A, Gyftopoulos K, Giannitsas K et al: Combination treatment with an alpha-blocker plus an anticholinergic for bladder outlet obstruction: a prospective, randomized, controlled study. J Urol 2003; **169:** 2253.
4. Kaplan SA, Roehrborn CG, Rovner ES et al: Tolterodine and tamsulosin for treatment of men with lower urinary tract symptoms and overactive bladder: a randomized controlled trial. JAMA 2006; **296:** 2319.
5. Wei JT, Calhoun E and Jacobsen SJ: Urologic diseases in America project: benign prostatic hyperplasia. J Urol 2008; **179:** S75.
6. Moher D, Cook DJ, Eastwood S et al: Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Lancet 1999; **354:** 1896.
7. Higgins JPT, Altman DG and Sterne JA: Assessing risk of bias in included studies. In: Cochrane Handbook for Systematic Reviews of Interventions, Version 5.1.0 (updated March 2011). Edited by JP Higgins and S Green. The Cochrane Collaboration 2011; chapt 8.
8. Barry MJ, Fowler FJ, O'Leary MP et al: The American Urological Association symptom index for benign prostatic hyperplasia. J Urol 1992; **148:** 1549.
9. Yamaguchi O, Kakizaki H, Homma Y et al: Solifenacin as add-on therapy for overactive bladder symptoms in men treated for lower urinary tract symptoms—ASSIST, randomized controlled study. Urology 2011; **78:** 126.
10. Thiessen-Philbrook H, Barrowman N and Garg AX: Imputing variance estimates do not alter the conclusions of a meta-analysis with continuous outcomes: a case study of changes in renal function after living kidney donation. J Clin Epidemiol 2007; **60:** 228.
11. Follmann D, Elliott P, Suh I et al: Variance imputation for overviews of clinical trials with continuous response. J Clin Epidemiol 1992; **45:** 769.
12. DerSimonian R and Laird N: Meta-analysis in clinical trials. Controlled Clin Trials 1986; **7:** 177.
13. Bradburn MJ, Deeks JJ, Berlin JA et al: Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. Stat Med 2007; **26:** 53.
14. Higgins JP and Thompson SG: Quantifying heterogeneity in a meta-analysis. Stat Med 2002; **21:** 1539.
15. Lee SH, Chung BH, Kim SJ et al: Initial combined treatment with anticholinergics and alpha-blockers for men with lower urinary tract symptoms related to BPH and overactive bladder: a prospective, randomized, multi-center, double-blind, placebo-controlled study. Prostate Cancer Prostatic Dis 2011; **14:** 320.
16. Chapple C, Herschorn S, Abrams P et al: Tolterodine treatment improves storage symptoms suggestive of overactive bladder in men treated with alpha-blockers. Eur Urol 2009; **56:** 534.
17. MacDiarmid SA, Peters KM, Chen A et al: Efficacy and safety of extended-release oxybutynin in combination with tamsulosin for treatment of lower urinary tract symptoms in men: randomized, double-blind, placebo-controlled study. Mayo Clin Proc 2008; **83:** 1002.
18. Kaplan SA, McCammon K, Fincher R et al: Safety and tolerability of solifenacin add-on therapy to alpha-blocker treated men with residual urgency and frequency. J Urol 2009; **182:** 2825.
19. Kaplan SA, Roehrborn CG, Gong J et al: Add-on fesoterodine for residual storage symptoms suggestive of overactive bladder in men receiving alpha-blocker treatment for lower urinary tract symptoms. BJU Int 2011; **109:** 1831.
20. Hollingsworth JM, Rogers MA, Kaufman SR et al: Medical therapy to facilitate urinary stone passage: a meta-analysis. Lancet 2006; **368:** 1171.
21. Sylvester RJ, Oosterlinck W and van der Meijden AP: A single immediate postoperative instillation of chemotherapy decreases the risk of recurrence in patients with stage Ta-T1 bladder cancer: a meta-analysis of published results of randomized clinical trials. J Urol 2004; **171:** 2186.
22. Athanasopoulos A, Chapple C, Fowler C et al: The role of antimuscarinics in the management of men with symptoms of overactive bladder associated with concomitant bladder outlet obstruction: an update. Eur Urol 2011; **60:** 94.
23. Blake-James BT, Rashidian A, Ikeda Y et al: The role of anticholinergics in men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia: a systematic review and meta-analysis. BJU Int 2007; **99:** 85.
24. Barry MJ, Williford WO, Chang Y et al: Benign prostatic hyperplasia specific health status measures in clinical research: how much change in the American Urological Association Symptom Index and the Benign Prostatic Hyperplasia Impact Index is perceptible to patients? J Urol 1995; **154:** 1770.