

ALTERNATIVE VIEWPOINTS

Pharmacoeconomic Evaluation of Antimuscarinic Agents: Bias toward Solifenacin?

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Ko and colleagues recently compared the cost-effectiveness of multiple antimuscarinic drugs for the treatment of overactive bladder (OAB),¹ including darifenacin, solifenacin, trospium, oxybutynin immediate release (IR), oxybutynin extended release (ER), transdermal (TD) oxybutynin, tolterodine IR, and tolterodine ER, using data from published clinical trials.^{2–7} They developed a decision-analysis model that included rates of discontinuation and treatment success, which they defined as complete continence as recorded in bladder diaries at the end of the trial. The model also included costs associated with OAB-induced comorbidities, which were estimated using the assumption that costs would be highest in patients who discontinued and lowest in patients who achieved treatment success. Their results suggest that the expected cost per patient and the cost-effectiveness ratio were lowest for solifenacin. However, closer examination of the relevant trials suggests that their analysis was biased toward solifenacin.

First, treatment success (i.e., continence) rates for solifenacin were derived from 3-day bladder diary data.⁶ Only 1 other study⁴ used 3-day bladder diaries, a head-to-head study of TD oxybutynin and tolterodine ER. Treatment success rates for tolterodine ER were calculated by pooling data from this study with data from a study³ in which 7-day diaries were used, weighted by the number of patients in each study

(the study in which 7-day diaries were used included more than 3 times as many patients). Treatment success rates for each of the other agents were derived exclusively from 7-day diary data.^{2, 3, 5, 7} This is problematic because it is well established that continence rates decrease as diary length increases (i.e., the likelihood of a patient having an incontinence episode becomes greater as the time that the patient is followed increases).⁸ Indeed, treatment success rates for tolterodine ER in the studies included by Ko and colleagues were 50% lower when a 7-day (17%) versus a 3-day diary (38%) was used. Thus, it is not surprising that treatment success rates were considerably higher for solifenacin and TD oxybutynin than for the other agents and, because success rate was a key factor in cost estimates, that the cost per patient and cost-effectiveness ratio were lowest for solifenacin and TD oxybutynin.

Second, the study populations may have differed in baseline demographic (e.g., age, gender) and clinical characteristics (e.g., baseline symptom severity, previous treatment with antimuscarinics) that influence treatment success rates. For instance, baseline frequency of incontinence episodes, which is inversely related to end-of-study continence rates,⁸ is provided in all reports that contributed to Ko and colleagues' analysis except for that of solifenacin.⁶ If baseline incontinence frequency was lower in the solifenacin study, this could result in higher treatment success rates. Again, this would bias the cost estimates favorably toward solifenacin.

Finally, the published report of the solifenacin study⁶ used by Ko and colleagues did not provide

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end-of-study continence rates for the placebo arm. This is problematic because placebo rates in clinical trials of OAB are notoriously large and variable,⁹ and differences between studies in placebo continence rates may reflect differences in study design.¹⁰ If the placebo effect in some antimuscarinic trials was larger than in others, this would also lead to artificially higher treatment success rates and, thus, bias the model.

If the considerations outlined above were controlled for in a subsequent analysis, the findings would likely be much different. Thus, further research on the relative cost-effectiveness of antimuscarinic drugs used in the treatment of OAB is needed.

References

1. Ko Y, Malone DC, Armstrong EP. Pharmacoeconomic evaluation of antimuscarinic agents for the treatment of overactive bladder. *Pharmacotherapy*. 2006;26(12):1694–1702.
2. Drutz HP, Appell RA, Gleason D, Klimberg I, Radomski S. 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):283–289.
3. 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;78(6):687–695.
4. Dmochowski RR, Sand PK, Zinner NR, et al. Comparative efficacy and safety of transdermal oxybutynin and oral tolterodine versus placebo in previously treated patients with urge and mixed urinary incontinence. *Urology*. 2003;62(2):237–242.
5. Zinner N, Gittelman M, Harris R, et al. Trospium chloride improves overactive bladder symptoms: a multicenter phase III trial. *J Urol*. 2004;171(6 Pt 1):2311–2315.
6. Cardozo L, Lisek M, Millard R, et al. Randomized, double-blind placebo controlled trial of the once daily antimuscarinic agent solifenacin succinate in patients with overactive bladder. *J Urol*. 2004;172(5 Pt 1):1919–1924.
7. 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;95(7):993–1001.
8. Wein AJ, Khullar V, Wang JT, Guan Z. Achieving continence with antimuscarinic therapy for overactive bladder: effects of baseline incontinence severity and bladder diary duration. *BJU Int*. 2007;99(2):360–363.
9. van Leeuwen JH, Castro R, Busse M, Bemelmans BL. The placebo effect in the pharmacologic treatment of patients with lower urinary tract symptoms. *Eur Urol*. 2006;50(3):440–453.
10. Staskin DR, Wein A. Is it possible to make cross-study comparisons of urinary continence rates in patients with overactive bladder? *Curr Med Res Opin*. 2005;21(6):835–837.

Authors' Reply

We appreciate the comments of Dr Hubbe. First, we would like to emphasize that we have no financial interests in any of the medications included in our analysis. This analysis was not supported by any manufacturer or other entity.

As such, we did not intend to bias our analysis toward or against any product. We agree with Dr. Hubbe regarding the potential influence of different definitions/measures for complete continence on the study results. His comments highlight the issue for meta-analysis and pharmacoeconomic research of treatment outcomes being measured slightly differently among studies, even though the same terminology is used. Additionally, pharmaceutical companies may select different endpoints to discourage direct comparisons.^{1, 2} Along those same lines, pharmaceutical manufacturers often select inappropriate comparison groups.³

Dr. Hubbe also raised the concern about the differences in study populations and in continence rate of the placebo arm among the studies that contributed to our analysis. This again, is another tactic used by some manufacturers to prevent direct or indirect comparisons. The problem is further compounded by the manufacturers providing insufficient information about the study design, methods, or analytical techniques. We acknowledge the potential influence of the differences on the analysis results. That is why we conducted sensitivity analyses by varying point estimates of treatment effect by $\pm 50\%$. Due to the limited data reported in the published studies, it is impossible to fully assess the comparability of study populations or the study designs between the studies. In addition, although it would have been ideal to adjust the continence rates for any placebo effect, this was not possible because half of the studies included in our analysis either fail to report continence rate for the placebo arm or did not include placebo arm in the clinical trial.

Finally, we agree with Dr. Hubbe that continuing and further research on the cost-effectiveness of antimuscarinic drugs for the treatment of OAB is needed, especially based on studies involving direct head-to-head comparisons. In the meantime, payers and health care organizations are forced to make decisions concerning formulary acceptance, placement, and other pharmacy benefit management techniques when confronted with marketed products. These decisions occur with and without the benefit of studies like the one we reported in *Pharmacotherapy*. Our goal in conducting studies like this is to assist payers in making decisions that explicitly take into account all known information. Although our

analysis is limited by the reported data, we believe that is better than making decisions in the absence of information.

References

1. Dmochowski R, Staskin D. Mixed incontinence: definitions, outcomes, and interventions. *Curr Opin Urol* 2005;15:374–9.
2. Adriaensen H, Plaghki L, Mathieu C, Joffroy A, Vissers K. Critical review of oral drug treatments for diabetic neuropathic pain—clinical outcomes based on efficacy and safety data from placebo-controlled and direct comparative studies. *Diabetes Metab Res Rev* 2005;21:231–40.
3. Psaty BM, Weiss NS. NSAID trials and the choice of comparators—questions of public health importance. *N Engl J Med* 2007;356:328–30.

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