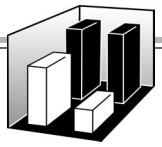
CLINICAL TRIALS REPORT



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Solifenacin Versus Tolterodine—A Head-to-Head Study: Finally! But Not Final?

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, **48**:464–470. http://www.sciencedirect.com. Accessed August 3, 2005.

Rating: •Of importance.

Introduction: To compare two new-generation antimuscarinics at their recommended doses for the treatment of overactive bladder (OAB) syndrome.

Aims: A prospective, double-blind, double-dummy, two-arm, parallel-group, 12-week study was conducted to compare the efficacy and safety of solifenacin 5 or 10 mg and tolterodine extended-release (ER) 4 mg once daily in patients with OAB.

Methods: After 4 weeks of treatment, patients had the option to request a dose increase, but were dummied throughout because approved product labeling only allowed an increase for those on solifenacin.

Results: Solifenacin, with a flexible dosing regimen, showed greater efficacy than tolterodine in decreasing urgency episodes, incontinence, urge incontinence, and pad usage and in increasing the volume voided per micturition. More of the patients who were treated with solifenacin became continent and reported improvements in perception of bladder condition assessments. Most of the side effects were mild to moderate in nature; discontinuations were comparable and low in both groups.

Discussion: Solifenacin, with a flexible dosing regimen, was found to be superior (according to the authors) to tolterodine ER with regard to most of the efficacy variables.

Editor's comments

In the United States, clinicians are blessed with the choice of six branded products for OAB syndrome (ER oxybutynin as a pill or patch, tolterodine, solifenacin, darifenacin, and trospium). However, after valiantly but vainly attempting to compare these formulations by analyzing "theoretical and marketing science," "apples-to-oranges" phase-3 studies, and clinical experience with their patients, there is no clear winner. To provide further answers, most clinicians would advocate for a head-to-head, double-blinded, placebo-optional study of a non-biased population with OAB syndrome. Is this realistic? Would more objective and meaningful comparative data be forthcoming from a head-to-head study or would the data that are generated be wrought with additional confounding issues? Could the conclusions from a head-to-head study be biased? Would a head-to-head study pose more questions than answers?

Only two studies have legitimately fulfilled the criteria stated previously for head-to-head studies: the OBJECT study [1] and the OPERA study [2], which compared single fixed dosages of ER oxybutynin (10 mg) and tolterodine (2 mg) twice daily and tolterodine (4 mg) long-acting, respectively. The debate that followed publication of these two studies questioned the inclusion and exclusion criteria, data-set selection, statistical analysis methodology, and ultimately the conclusions that were drawn. A great sacrifice had been made by ALZA (Mountain View, CA) and Ortho-McNeil (Raritan, NJ) to the 'gods of clinical science' and physician expectations, but there was no sign from 'mount IMS' (http://www.imshealth.com/ims/portal/front/indexC/0,2478,6599_1825,00.htm) that there was a clear winner measured by the change in market share. Are the ghosts of OBJECT and OPERA harbingers of the debate that will follow this paper? The following sections preview four issues without giving away the ending.

The first issue is that 4 weeks after this study, "patients had the option of either continuing with their original dose or requesting a dose increase based on their satisfaction with treatment efficacy and tolerability, and discussions with the investigator." The rationale for this study design is that there is only one approved dosage of tolterodine long-acting. In addition, in the discussion section, the authors state that "the trial design allowed patients to request an increase in the study medication dose after 4 weeks if they thought their treatment was suboptimal."

Is it meaningful to compare a single dose of one drug (tolterodine ER 4 mg) with two escalating doses of another drug (solifenacin 5 mg increasing to 10 mg)? If performed in this manner, should the efficacy and side effects be broken down for each drug at each dose?

The primary debate may center on this type of study design and statistical analysis—the dosage increase of solifenacin and the 'pooling' of the solifenacin efficacy and tolerability results. In real life, patients have the efficacy:tolerability ratio of one dosage or another. Assuming that the 5-mg solifenacin has lower efficacy and the 10-mg solifenacin has lower tolerability, the method of increasing the dosage is transparent. However, wouldn't independent comparisons between ER tolterodine 4 mg versus solifenacin 5 mg and ER tolterodine 4 mg versus solifenacin 10 mg be more useful? Does the effect of pooling highlight the efficacy difference, but put the tolerability results of the study in the shadows? The authors highlight the efficacy superiority without mentioning the higher adverse effects ("the majority of side effects were mild to moderate in nature") in the abstract, but, by pooling the adverse effects, do they diminish the actual numbers for the individuals taking 10-mg solifenacin?

The second issue is that 51% of the patients taking tolterodine 4 mg and 48% of those taking solifenacin 5 mg requested a dose increase.

The debate may center (according to the authors) on the fact that approximately 50% of the patients requested an increase in their dosage. Taken together, these findings could suggest that patients may be less tolerant of a lack of efficacy than of antimuscarinic adverse effects. The authors state that "these aspects are important, as effective treatment should provide an optimal balance of maximum achievable improvement in clinical symptoms coupled with acceptable tolerability and thereby an identifiable and worthwhile improvement in QOL [quality of life]."

Of interest, MacDiarmid [3] reviewed the data from two dose-escalation studies [4,5] regarding oxybutynin ER. It was demonstrated that 48% to 65% of patients would increase their dose higher than oxybutynin ER 10 mg to achieve continence. This is a higher dosage than what was used in the OPERA and OBJECT studies. MacDiarmid [3] stated that "when patients are given the option to increase the dose of their medication to achieve the best balance between efficacy and side effects, they often choose higher dosages than 5 and 10 mg of oxybutynin-ER. In contrast, most prescriptions in the United States are for 5 or 10 mg. According to nationwide prescription data (data on file, Ortho-McNeil), the percentage of 5-mg, 10-mg, and 15-mg prescriptions written by health care providers are 41%, 48%, and 11%, respectively." In real life, it appears that few physicians dose-adjust for maximal benefit for this condition [3].

An additional issue is that the debate may center on the primary and secondary outcome variables and the statistical methodology to determine the outcomes. The primary outcome variable in the study was a "non-inferiority comparison of the change from baseline to endpoint in the mean number of micturition per 24 hours" [4]. Patients received the same double-dummied treatment capsules. The debate may center on encapsulation issues with the 'dummy' pills based on 'dissolution' rather than 'pharmacokinetic' studies.

The company (Yamanouchi, now Astellas [Japan]) and the investigators deserve our respect and admiration for an interesting study design and completion of the study, and for their contribution to the general knowledge of OAB (and the individual and comparative information about these two medications). The readers are strongly encouraged to familiarize themselves with this paper to join in the analysis and the debate.

References

1. 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, **76:**358–363.
2. 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:**687–695.
3. MacDiarmid SA: **Overactive bladder: improving the efficacy of anticholinergics by dose escalation.** *Curr Urol Rep* 2003, **4:**446–451.
4. Anderson RU, Mobley D, Blank B, *et al.*: **Once-daily controlled versus immediate-release oxybutynin chloride for urge urinary incontinence.** *J Urol* 1999, **161:**1809–1812.
5. Gleason DM, Susset J, White C, *et al.*: **Evaluation of a new once-daily formulation of oxybutynin for the treatment of urinary urge incontinence.** *Urology* 1999, **54:**420–423.