A meta-analysis comparing trials of antimuscarinic medications funded by industry or not

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Accepted for publication 27 March 2006

OBJECTIVE

To determine if there is a significant difference in outcomes of clinical trials funded by industry or not of antimuscarinic medications used to treat overactive bladder (OAB) symptoms and detrusor overactivity (DOA).

METHODS

A Medline search was conducted from January 1966 to June 2003 to identify human clinical trials of oxybutynin and tolterodine published in English. Randomized controlled trials on subjects aged ≥16 years who were being treated with oxybutynin or tolterodine for OAB symptoms or DOA; 24 studies were identified. The endpoints assessed were OAB symptoms or changes in uninhibited detrusor contractions on cystometrography. The outcome variables were dichotomized as 'improvement' or 'no improvement'. Odds ratios and 95% confidence intervals were calculated for each study based on data derived or extracted from tables and figures.

RESULTS

Meta-analysis showed no significant difference in the outcomes trails funded by industry or not. Trials were then reviewed to determine their adherence to the Consolidated Standards of Reporting Trials (CONSORT) guidelines for randomized trials.

CONCLUSIONS

Clinical trials are important for clinicians when selecting medical therapies. In this analysis we found no difference in outcomes when comparing studies funded by industry or not for tolterodine and oxybutynin. The quality of all trials would be improved by close adherence to the CONSORT guidelines for randomized clinical trials.

KEYWORDS

overactive bladder, urinary incontinence, urge incontinence, treatment outcomes, funding

INTRODUCTION

Overactive bladder (OAB) is the symptom complex of urinary urgency, frequency and urge incontinence, and affects ≈9% of adults in the USA [1]. Treatments available for OAB include behavioural interventions, pelvic muscle exercises, medications and surgery. Antimuscarinic medications are commonly used to treat OAB symptoms.

Pharmaceutical companies have invested millions of dollars in clinical trials to evaluate these medications [2]. In 2002 the pharmaceutical industry spent more money on research and development of new drugs than the entire USA National Institutes of Health operating budget [5]. When a company sponsors a study in which they have a primary financial interest, a potential conflict of interest occurs.

Studies evaluating clinical trials for NSAIDs and for antidepressant medications have found that those funded by pharmaceutical companies were more likely than publicly funded studies to have outcomes that favour the sponsor [3,4]. The purpose of the present study was to evaluate the outcomes of clinical trials of antimuscarinic medications used to treat urinary urgency, frequency and urge incontinence, to determine if there is an effect based on funding source.

METHODS

The Hartford Hospital Institution Review Board approved this study. A Medline search was conducted from January 1966 to June 2003 to identify human clinical trials of oxybutynin and tolterodine published in English. Article references were cross-referenced with the search results and any missing trials were identified.

The reports were assessed in a meta-analysis to determine if studies funded by the pharmaceutical industry had significantly different outcomes deemed as ($P < 0.05$). Inclusion criteria for the analysis were human randomized clinical trials (RCTs) on subjects aged ≥16 years who were being treated for OAB symptoms or detrusor overactivity (DOA). Exclusion criteria were studies of non-oral medications, dose-ranging evaluations, meta-analyses and nonrandomized trials; 24 studies which met the inclusion criteria are included in the present analysis.

For clinical heterogeneity, all the studies in this analysis evaluated the effect of tolterodine and oxybutynin in the treatment of OAB symptoms. Subjects were both male and female, with an age range of 16 to >90 years. Some studies had an age range of >65 years. Criteria for entering these studies included OAB symptoms or DOA documented by cystometrography. The endpoints assessed were OAB symptoms or changes in uninhibited bladder contractions on cystometrography.

All of the studies were RCTs; most were placebo-controlled trials but some involved crossover trials and others had several treatment groups. Some of the data needed to be calculated or estimated and therefore the 95% CIs were based only on those estimates. Odds ratios and effect sizes for several of the studies might have been slightly

different than if the actual data had been used.

The outcome variable was dichotomized as 'improvement' or 'no improvement'. In four studies funded by pharmaceutical companies, parallel designs (i.e. no placebo control) were used. When this occurred, the sponsor's product was considered to be the treatment and the other medication was considered as the control.

Studies were reviewed to determine their overall quality. The basis for this assessment was the guidelines from the Consolidated Standards of Reporting Trials (CONSORT) [5] recommendations for randomized trials. Seventeen of these criteria were used to standardize reporting.

RESULTS

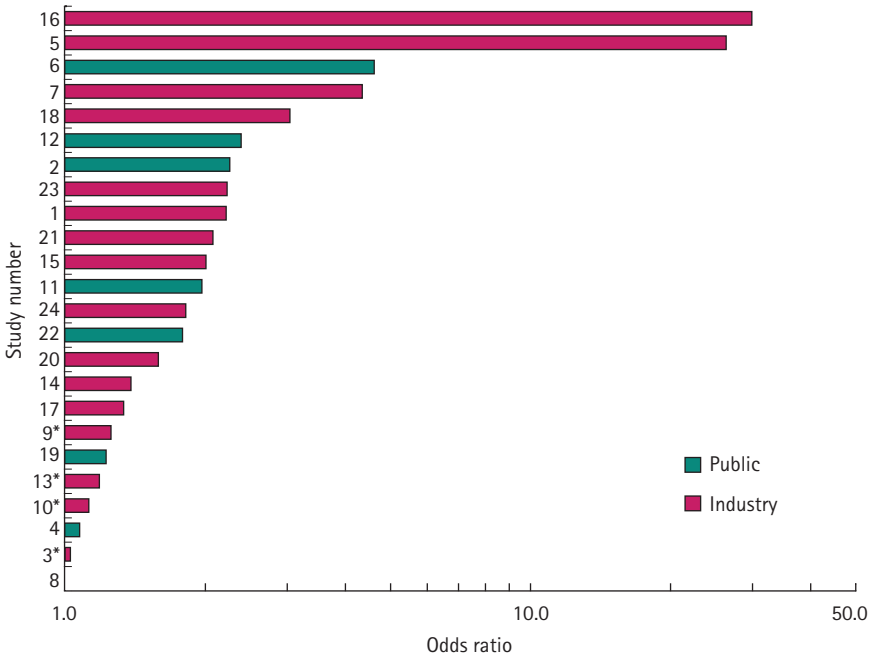
Twenty-four studies met the inclusion criteria for the present analysis; 15 were sponsored by industry and nine were funded by public sources. There was no significant difference between the study groups (Fig. 1) [6–29]. Both oxybutynin and tolterodine were more effective than placebo. Four studies compared oxybutynin and tolterodine directly: one reported that oxybutynin was more effective; one reported that tolterodine was more effective; and the other two reported no significant difference in outcomes.

For the quality of these studies, neither group conformed completely to the CONSORT guidelines (Fig. 2). The publication dates of the publicly funded studies were earlier on average than those of the industry-funded studies.

DISCUSSION

Clinical trials are used to determine the safety and efficacy of medications in specific populations; pharmaceutical companies fund many of these studies. It is reassuring that the present analysis detected no significant difference in the outcomes of trials based on the funding source. Neither group of studies (funded by pharmaceutical industry or not) followed all of the CONSORT guidelines, but these guidelines were not published until 1998, and many of the studies used in this analysis (including most of those publicly funded) were published before 1998. In general, more recent studies were better at following the CONSORT guidelines. These simple guidelines are very effective for standardizing studies for quality, and for comparing results. Ultimately, adherence to these guidelines will improve patient care.

*FIG. 1. Estimated odds ratios for studies reporting an improvement with drug vs placebo. *Study used a parallel design (no placebo).*



There are several other potential sources of bias in these studies that we were unable to assess. It is possible that although a study was funded with no pharmaceutical industry funds, the authors might have had other interests in the pharmaceutical industry that were not reported (paid speakers, membership on advisory boards).

There is a bias towards publishing studies that have only positive results. In the present analysis, two of the nine privately funded studies showed no significant benefit with medication. All 15 industry-funded studies showed a significant improvement ($P < 0.05$) with medication. Studies that showed no significant improvement with medication might not be published.

Bias can also occur when selecting the outcomes used to determine clinical effectiveness. For example, to determine if a medication is effective in reducing urinary frequency the frequency of voids/24 h could be assessed. If there is no statistical improvement in this outcome, a different outcome, e.g. voids per week, might be reported. Ideally the outcomes to be analysed should be determined before initiating the study. All other outcomes should be reported as a *post hoc* analysis.

A further bias might arise from language or country of publication [30]. In the present study several of the publications were based on research conducted at foreign (i.e. not in the USA) sites. Several were multinational clinical trials, for which participating centres were in countries where English is not the primary language. Although all of the trials we included were written in English, the broad scope of countries participating in these studies makes the results more generally applicable.

There are many other medications available to treat urinary urgency, frequency and urge incontinence. We analysed trials of tolterodine and oxybutynin because they were included in the most RCTs available for these two medications.

In conclusion, pharmaceutical industry-funded research might be helpful to clinicians when selecting medical therapies. In the present analysis we found no difference in outcomes when comparing industry-funded studies to publicly funded studies for tolterodine and oxybutynin. All studies could

FIG. 2. Adherence to CONSORT Guidelines. Green filled circles, Yes; red open circles, No; –, N/A.

Study	Placebo controlled	Hypothesis stated	Primary end points determined prior to study	Primary end points clearly defined	Eligibility criteria stated	Sample size calculation	Power calculation done	Method of randomization stated	Blinded study	Statistical methods of primary outcomes stated	Statistical methods of subgroups stated	Number of patients beginning trial reported	Number of patients receiving intended treatment stated	Baseline demographics reported	Estimate of effect size reported for each outcome	Any multiple comparisons stated	Adverse events reported
INDUSTRY																	
[21]	●	○	–	○	●	○	○	○	●	○	○	●	●	○	○	–	●
[6]	●	○	○	○	●	●	○	●	●	●	–	●	●	●	●	–	●
[20]	●	●	–	○	●	○	○	●	●	●	●	●	●	●	●	–	●
[12]	●	●	○	○	●	●	●	○	●	●	●	●	●	○	●	–	●
[22]	●	●	–	●	●	●	●	○	●	●	●	●	●	●	●	–	●
[19]	●	●	●	●	●	○	●	○	●	●	●	●	●	●	○	–	●
[26]	●	●	●	●	●	○	○	●	●	●	●	●	●	●	●	–	●
[28]	●	●	●	●	●	○	○	○	●	●	●	●	●	●	●	●	●
[25]	●	●	○	○	●	○	○	○	●	●	●	●	●	●	●	–	●
[23]	●	●	○	○	●	●	●	○	●	●	●	●	●	●	●	–	●
[15]	○	○	–	●	●	○	○	●	●	●	●	●	●	●	●		●
[18]	○	●	●	●	●	●	●	●	●	●	●	●	○	●	●	–	●
[8]	○	●	–	●	●	●	●	●	●	●	●	●	●	●	●	–	●
[14]	○	●	●	●	●	○	○	●	●	●	●	●	●	●	●		●
[29]	●	●	–	●	●	●	●	●	●	●	●	●	●	●	●	●	●
NON-INDUSTRY																	
[11]	●	○	○	○	○	○	○	○	●	○	○	●	●	○	○	–	●
[7]	●	○	○	○	●	○	○	●	●	●	●	●	●	●	○	–	●
[13]	●	–	○	○	●	○	●	○	●	●		●	●	some	●	–	●
[10]	●	●	○	○	●	○	○	●	●	○	●	●	●	●	○	–	●
[24]	●	●	●	●	●	○	○	○	●	○	○	●	●	●	●	–	●
[17]	●	●	–	●	●	○	○	●		●	●	●	●	●	●	–	●
[16]	●	●	–	○	●	●	●	●	●	●	●	●	●	●	○	–	●
[27]	●	●	–	●	●	○	○	○	●	●	●	●	●	●	●	–	○
[9]	●	●	–	○	●	○	○	○		–	●	●	●	●	●	–	○

be improved by strict adherence to the CONSORT guidelines for RCTs.

CONFLICT OF INTEREST

P. K. Tulikangas: Speakers Bureau-Pfizer.

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Abbreviations: **OAB**, overactive bladder; **DOA**, detrusor overactivity; **RCT**, randomized controlled trial; **CONSORT**, Consolidated Standards of Reporting Trials.