Publication Bias in the Pulmonary/Allergy Literature: Effect of Pharmaceutical Company Sponsorship

Howard Liss MD

Rokach Center for the Prevention of Lung Diseases, Clalit Health Services, and Tuberculosis Treatment and Prevention Unit, Jerusalem, Israel

Key words: pharmaceutical industry, clinical trials, drug studies, ethics

Abstract

Background: A publication bias exists towards positive results in studies funded by pharmaceutical companies.

Objectives: To determine whether drug studies in the pulmonary/allergy literature also demonstrate a publication bias towards more favorable results when a pharmaceutical company funds the study.

Methods: We reviewed all original articles published in seven pulmonary and allergy journals between October 2002 and September 2003. Included in the review were studies of inhaled corticosteroids (oral or nasal), long- or short-acting bronchodilators, or leukotriene receptor antagonists. Articles with funding from a pharmaceutical company and/or one or more authors employed by a pharmaceutical company were considered pharmaceutical company-sponsored studies. The remaining studies were considered not sponsored by a pharmaceutical company. Results were compared to ascertain whether positive results were obtained more frequently in the company-sponsored studies.

Results: Of the 100 articles included in this review 63 were considered pharmaceutical company-sponsored research. Results favorable for the drugs studies were significantly more common in those funded by a pharmaceutical company (98% vs. 32%).

Conclusions: In the pulmonary and allergy literature, as in other fields, there is a publication bias towards positive results in pharmaceutical company-sponsored research.

IMAJ 2006;8:451–454

For Editorial see page 494

Representatives of pharmaceutical companies visit physicians to encourage use of their company's drugs. To support the claim of their drug's superiority they often present literature; this literature is usually funded by their pharmaceutical company. It is known that results of studies that are funded by pharmaceutical companies are biased in favor of the funding company [1]. To the best of our knowledge no studies have yet been done on pharmaceutical company-sponsored research in allergy or pulmonary medicine. This study was designed to review published studies of drugs we commonly use in our pulmonary/allergy clinic to determine whether the results of studies with pharmaceutical company funding were more favorable than those of similar studies not funded by such a company.

Methods

The following journals were reviewed: *Allergy*, *American Journal of Respiratory and Critical Care Medicine*, *Annals of Allergy Asthma and Immunology*, *Chest*, *European Respiratory Journal*, *Journal of Allergy and Clinical Immunology*, *Respiratory Medicine*, and *Thorax*. From these we extracted and read all original articles published between October 2002 and September 2003. These included studies of nasal or oral inhaled corticosteroids, long- or short-acting bronchodilators, and leukotriene receptor antagonists. Review articles, meta-analyses, letters, editorials, and case reports were not included.

Articles were considered to be pharmaceutical company-sponsored studies if the funding and/or at least one author was from the pharmaceutical company. Otherwise, they were considered non-pharmaceutical company-sponsored studies. Other financial benefits to the authors, such as honoraria, travel, consulting fees, or other research grants were not considered funding for that particular study.

Results were considered favorable if the study drug was more effective than a placebo or a comparator drug, or if the patients' condition clinically worsened when the drug was removed. If a second drug was added to a treatment regimen without further clinical or laboratory improvement, the results were considered favorable for the original drug. Studies that used only one drug were automatically considered to have favorable results. An unfavorable study showed a side effect of the drug or the drug was not more effective than a placebo or comparator drug.

Studies were classified as clinical or non-clinical. Clinical studies measured symptoms, pulmonary function tests, financial considerations, use of medical resources such as doctor or emergency room visits, early or late asthma response, survival, or some other measure of patient well-being. Studies of inflammatory markers, cytokine release, airway hyper-responsiveness, or bronchoscopy biopsies were considered non-clinical.

Results

Altogether, 1846 articles were reviewed. Of these, 100 (5.4%) studied inhaled corticosteroids (oral or nasal), long- or short-acting bronchodilators, or leukotriene receptor antagonists [Table 1]. Pharmaceutical companies funded 63 of these studies. Thirty-

Table 1. Research articles on drugs published in the pulmonary literature, October 2002 to September 2003

Journal	Total no. of studies	With pharmaceutical company funding	Without pharmaceutical company funding
Allergy	105	1	3
Ann Allergy Asthma Immunol	117	7	4
Am J Respir Crit Care Med	333	6	3
Chest	443	8	7
Eur Respir J	285	12	6
J Allergy Clin Immunol	260	10	4
Respir Med	170	13	8
Thorax	133	6	2
Total	1846	63	37

Study drugs included inhaled (oral or nasal) corticosteriods, long- or short-acting bronchodilators, and leukotrience receptor antagonists

seven studies had non-pharmaceutical company funding or did not list any funding source and were considered non-pharmaceutical company-sponsored studies.

Of the sponsored studies, 19 had funding from the pharmaceutical companies only, 10 did not list pharmaceutical company funding but at least one author was an employee of such a company, and 34 studies had both, i.e., were funded and the authors were employed by a pharmaceutical company. The companies represented in these studies were GlaxoSmithKline (30 studies), Astra-Zeneca (12 studies), Merck (9 studies), Boehinger (4 studies), Forest Labs (2 studies), Novartis (2 studies), and Sepacor, BykGulden, 3M, and DracoLake Med (1 study each).

Of the 63 sponsored studies, 62 (98%) had results favorable for the drug or drugs of the funding company. The percent of favorable studies was significantly lower when there was no pharmaceutical company funding, with only 12 of 37 (32%) of the non-sponsored studies having positive results for the drugs studied ($P < 0.05$ by chi-square). In addition, the sponsored studies included significantly more clinical studies: 54 of the 63 (82%) were clinical compared to only 23 of the 37 non-sponsored studies (62%) ($P < 0.05$ by chi-square).

Discussion

We found that in 62 of the 63 studies funded by the pharmaceutical companies the results were favorable for the funding company. The question that has to be asked is: how do the pharmaceutical companies ensure that only favorable results of their drugs are published? Clearly, there are certain biases in pharmaceutical company-sponsored research that can distort the efficacy of their drugs [2].

Biases in protocols

Pharmaceutical companies fund large studies only after a smaller pilot study has shown favorable results. Possibly, only the more promising variables derived from the pilot study are included in the larger study's protocol. The larger study is therefore confirmatory rather than exploratory and is undertaken to confirm the funding company's biases and maximize the chances of favorable results. For example, two studies with similar protocols examined the addition of montelukast on markers of inflammation in asthmatics already taking inhaled fluticasone. In the study funded by GlaxoSmithKline (United Kingdom), the producers of fluticasone, the markers included changes in mast cells, CD45KO, and activated eosinophils on bronchial biopsies [3]. They found no change with the addition of montelukast. In another university-funded study, lung function was not improved, but markers of inflammation, including adenosine monophosphate threshold, recovery, exhaled nitrous oxide, and blood eosinophils, did improve [4]. The findings of the study sponsored by the pharmaceutical company were favorable to the funding company, while those of the study not sponsored by a pharmaceutical company would not have been favorable to GlaxoKlineSmith, even though the same drugs were studied in a similar fashion.

Bias can also be introduced by using an inappropriate comparator drug. In the treatment of allergic rhinitis, leukotriene receptor antagonists are equal to non-sedating antihistamines, and both are definitely inferior to intranasal corticosteroids [5]. However, an article demonstrating that montelukast was effective in allergic rhinitis presented data only comparing montelukast against placebo. There were no data showing how montelukast fared against either loratadine or the accepted treatment of intranasal corticosteroids.

An inappropriate control group may also bias the results. In another study, asthmatic patients unstable on inhaled corticosteroids were given either fomoterol or terbutaline as needed [7]. The article concludes that fomoterol is a better rescue medication than terbutaline. However, the article states: "It has to be emphasized that the patients in the present study all received moderate to high doses of inhaled corticosteroids and in addition had a daily need for rescue treatment of at least three times/day at randomization, which means that according to present guidelines, this patient group would all be prescribed a maintenance use of long acting beta-agonists." Treatment with fomoterol was the appropriate next step in the care of these patients and the terbutaline arm was inappropriate.

Unfavorable studies are not published

To keep unfavorable results from being published, the funding companies try to control the data that are generated and influence the writing and editing of manuscripts. The final decision to publish may be made by the pharmaceutical company and not the investigators, and it is possible that negative studies are not submitted for publication. This interference may or may not be acceptable to the institution conducting the research [8]. Although there are guidelines to minimize pharmaceutical company interference [9], their acceptance is not uniform [10].

The pressure to suppress negative results may have influenced the results of this review, where unfavorable studies were found only in studies not funded by a pharmaceutical company. Four articles demonstrated side effects of inhaled corticosteroids, including an increase in hip fractures [11], adrenal suppression in children [12,13], and oral candidiasis [14]. Another study could not show that levalbuterol was any better than conventional

nebulized bronchodilators in chronic obstructive pulmonary disease [15], and one study failed to demonstrate the usefulness of oral montelukast in acute asthma [16].

Overstating claims

In several articles the authors made claims about a drug's efficacy that were not supported by the data. A study of asthmatic children concluded that ICS were as effective as oral corticosteroids for the week following an acute attack [17]. The article concludes: "ICS were found to be useful in the management of acute asthma in children; however, spirometry data suggested a more rapid resolution of asthma with OCS." In fact, the data clearly show that on days 3 and 7, the improvement in spirometry was significantly greater with OCS.

Another study compared formoterol and terbutaline as rescue medications in asthmatic patients treated with formoterol and ICS twice daily [18]. There were no differences in symptoms, time to first exacerbation, use of rescue medication, or pulmonary function tests regardless of which rescue medication was used. The authors admit that using formoterol would be more expensive, but still recommended that the question be studied further.

Other articles studied the use of ICS in chronic obstructive pulmonary disease. In one article, fluticasone was given in COPD and the authors concluded that it was better than placebo and was a cost-effective treatment [19]. They based their conclusions on the fluticasone group having a significantly larger increase in forced expiratory volume in the first second than did the placebo group. They accepted a 10% increase in FEV1 as significant because they claimed that a 10% increase is the minimum improvement that can be perceived by asthmatics. But the study they cite as support for this showed that the improvement in FEV1 had to be at least 230 ml to be perceived [20]. In this study of moderate to severe COPD with a mean FEV1 of 1.5–1.6 L, a 10% increase would not reach this threshold. Secondly, only 32% of the patients receiving fluticasone and only 19% of patients receiving placebo improved their FEV1 by 10%. While these numbers may be statistically significant, their clinical significance is far from clear.

Another study claimed that stopping ICS in patients with COPD led to more rapid and more frequent exacerbations and deterioration in aspects of their quality of life [21]. It is true that during the study period the patients whose ICS was stopped did have their first exacerbation sooner. Overall, 57% of patients who had ICS stopped did have an exacerbation. However, 47% of patients who continued ICS also had an exacerbation. Again, while these numbers may be statistically significant, their clinical significance is unclear, with so many patients in both groups having exacerbations. In addition, continuing or discontinuing ICS had no effect on FEV1, 6 minute walk, or Borg scale of breathlessness.

To be fair, the problem of overstating the significance of the data was not unique to the pharmaceutical company-sponsored studies. One example was found in the group of studies not sponsored by a pharmaceutical company [22]. In a study of salbutamol and salmeterol in exacerbations of COPD, the abstract concludes: "These data indicate that salmeterol is effective and safe in the treatment of acute exacerbation of COPD and support its use in this clinical condition." However, the last line of the article states: "Therefore, the real benefits and risks of salmeterol in the treatment of acute exacerbations of COPD will only be determined by carefully designed clinical studies."

Redundant publication

Reporting data similar to those of a previously published study with a favorable outcome ensures positive results. In an article that studied fluticasone propionate 250 µg once daily in asthmatics [23], the abstract begins: "Studies have shown fluticasone propionate 100, 200, and 500 µg administered once daily to be effective in the treatment of asthma. The efficacy of a once daily regimen of fluticasone propionate 250 µg has not been evaluated previously." Another study with an intermediate dose of fluticasone is redundant and unnecessary, although it most likely assures another pharmaceutical company-sponsored study with positive results.

Financial ties to pharmaceutical companies

Aside from receiving pharmaceutical company funding for a specific study, many authors also receive other monetary perks from these companies, such as honoraria for talks, money for travel, consulting fees, stock in the funding company, or other research or educational grants. The simple fact that a potential financial conflict of interest exists is enough to bias the results of these studies towards more favorable results for the funding company [24]. To avoid this, many journals now require that authors disclose their financial ties with pharmaceutical companies. Physicians seem to pay attention to these disclosures, and articles are believed less when readers suspect a potential conflict [25]. A conflict of interest is even more likely when authors are employed by a pharmaceutical company, which occurred in 44 of the 63 company-sponsored studies (70%).

Eighty-two of the 100 studies were randomized controlled trials. However, there are certain ethical considerations when designing and performing an RCT. Ideally, the investigator does not know or have an interest in which treatment arm is better. In reality, the pharmaceutical companies and their investigators often have opinions and expectations regarding the various treatment arms and a financial interest in the outcome. This in itself may not necessarily invalidate the RCT. But these biases may influence how the research is done and the results obtained. If the study design includes an inappropriate treatment arm, inferior comparator drug, or inappropriate control groups, then the RCT could be invalid, or even unethical to perform.

ICS = inhaled corticosteroids
OCS = oral corticosteroids
COPD = chronic obstructive pulmonary disease
FEV1 = forced expiratory volume in the first second
RCT = randomized controlled trial

Conclusions

In this survey, almost all published studies sponsored by a pharmaceutical company had results favorable to the funding company. This bias probably stems from the efforts of the pharmaceutical companies to ensure that only studies favorable to their drug are published.

Funding clinical trials is one way that pharmaceutical companies promote their drugs. They legitimately want a good return on this investment, and publishing favorable studies is to their benefit. It is these studies, published in the literature, that company representatives present when visiting physicians. Since clinical studies may have more of an impact on prescribing habits, it is not surprising that there were significantly more clinical studies among those sponsored by pharmaceutical companies.

We must acknowledge that there may be a publication bias towards positive results in studies funded by pharmaceutical companies. In this series, the results of the company-sponsored studies could be predicted just by looking at which pharmaceutical company funded the study. We must therefore look at the results of these studies as a tool used by the pharmaceutical companies to influence the practice of physicians and, hence, are potentially biased.

Acknowledgments. I thank Natalie Shlomo for statistical analyses and Drs. Moshe Finelt, Raphael Breuer and Shmuel Goldberg for comments on the manuscript.

References

1. Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: a systemic review. *Br Med J* 2003;326:1167–70.
2. Miller FG, Brody H. Professional integrity in industry-sponsored clinical trials. *Acad Med* 2005;80:899–904.
3. O'Sullivan S, Akveld M, Burke CM, Poulter LW. Effect of the addition of montelukast to inhaled fluticasone propionate on airway inflammation. *Am J Respir Crit Care Med* 2003;167:745–50.
4. Currie GP, Lee DKC, Haggart K, Bates CE, Lipworth BJ. Effects of montelukast on surrogate inflammatory markers in corticosteroid-treated patients with asthma. *Am J Respir Crit Care Med* 2003;167:1232–8.
5. Nathan RA. Pharmacotherapy for allergic rhinitis: a critical review of leukotriene receptor antagonists compared with other treatments [Review]. *Ann Allergy Asthma Immunol* 2003;90:182–91.
6. van Adelsberg J, Philip G, LaForce CF, et al. Randomized controlled trial evaluating the clinical benefit of montelukast for treating spring seasonal allergic rhinitis. *Ann Allergy Asthma Immunol* 2003;90:214–22.
7. Stahl E, Postma DS, Svensson K, et al. Formoterol used as needed improves health-related quality of life in asthmatic patients uncontrolled with inhaled corticosteroids. *Respir Med* 2003;97:1061–6.
8. Mello MM, Clarridge BR, Studdert DM. Academic medical centers' standards for clinical trial agreements with industry. *N Engl J Med* 2005;352:2202–10.
9. Davidoff F, DeAngelis CD, Drazen JM, et al. Sponsorship, authorship, and accountability. *N Engl J Med* 2001;345:825–7.
10. Schulman KA, Seil DM, Timbie JW, et al. A national survey of provisions in clinical trial agreements between medical schools and industry sponsors. *N Engl J Med* 2002;347:1335–41.
11. Hubbard RB, Smith CJP, Smeeth L, Harrison TW, Tattersfield AE. Inhaled corticosteroids and hip fracture: a population-based case-controlled study. *Am J Respir Crit Care Med* 2002;166:1563–6.
12. Goldberg S, Einot T, Algur N, et al. Adrenal suppression in asthmatic children receiving low-dose inhaled budesonide: comparison between dry powder inhaler and pressurized metered-dose inhaler attached to a spacer. *Ann Allergy Asthma Immunol* 2002;89:566–71.
13. Sim D, Griffiths A, Armstrong D, Clarke C, Rodda C, Freezer N. Adrenal suppression from high-dose inhaled fluticasone propionate in children with asthma. *Eur Respir J* 2003;21:633–6.
14. Fukushima C, Matsuse H, Tomari S, et al. Oral candidiasis associated with inhaled corticosteroid use: comparison of fluticasone and beclomethasone. *Ann Allergy Asthma Immunol* 2003;90:646–51.
15. Datta D, Vitale A, Lahiri B, ZuWallack R. An evaluation of nebulized levalbuterol in stable COPD. *Chest* 2003;124:844–9.
16. Cylly A, Kara A, Ozdemir T, Ogus C, Gulkesen KH. Effects of oral montelukast on airway function in acute asthma. *Respir Med* 2003;97:533–6.
17. Nakanishi AK, Klasner AK, Rubin BK. A randomized controlled trial of inhaled flunisolide in the management of acute asthma in children. *Chest* 2003;124:790–4.
18. Ind PW, Villasante C, Shiner RJ, et al. Safety of fomoterol by Turbuhaler as reliever medication compared with terbutaline in moderate asthma. *Eur Respir J* 2002;20:859–66.
19. Ayers JG, Price MJ, Efthimou J. Cost-effectiveness of fluticasone propionate in the treatment of chronic pulmonary disease: a double-blind randonized, placebo-controlled trial. *Respir Med* 2003;97:212–20.
20. Santanello NC, Zhang J, Seidenberg B, Reiss TF, Barber BL. What are minimal important changes for asthma measures in a clinical trial? *Eur Respir J* 1999;14:23–7.
21. van der Valk P, Monninkhof E, van der Palen J, Zielhuis G, van Herwaarden C. Effect of discontinuation of inhaled corticosteroids in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2002;166:1358–63.
22. Cazzola M, Califano C, Di Perna F, et al. Acute effects of higher than customary doses of salmeterol and salbutamol in patients with acute exacerbations of COPD. *Respir Med* 2002;96:790–5.
23. Berger WE, Ford LB, Mahr T, et al. Efficacy and safety of fluticasone propionate 250 mcg administered once daily in patients with persistent asthma treated with or without inhaled corticosteroids. *Ann Allergy Asthma Immunol* 2002;89:393–9.
24. Perlis RH, Perlis CS, Wu Y, et al. Industry sponsorship and financial conflict of interest in the reporting of clinical trials in psychiatry. *Am J Psychiatry* 2005;162:1957–60.
25. Chaudhry S, Schroter S, Smith R, Morris J. Does declaration of competing interests affect readers' perception? A randomized trial. *Br Med J* 2002;325:1391–2.

Correspondence: Dr. H. Liss, Rokach Center for the Prevention of Lung Diseases, 5 Sarei Street, Jerusalem 94390, Israel.
Phone: (972-2) 501-7555
Fax: (972-2) 538-5697
email: howardl@clalit.org.il