Adverse Effects of Inhaled Corticosteroids in Funded and Nonfunded Studies

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**Background**: Evidence regarding the safety profile of drugs may vary depending on study sponsorship. We aimed to evaluate differences between studies funded by the pharmaceutical manufacturer of the drug (PF) and those with no pharmaceutical funding (NoPF) regarding the finding and interpretation of adverse effects of inhaled corticosteroids.

**Methods**: We assessed the safety reporting of inhaled corticosteroids in 275 PF and 229 NoPF studies identified by a MEDLINE search using prespecified criteria.

**Results**: Overall, the finding of statistically significant differences for adverse effects was significantly less frequent in PF (34.5%) than in NoPF (65.1%) studies (prevalence ratio, 0.53; 95% confidence interval, 0.44-0.64). This association became nonsignificant (prevalence ratio, 0.94; 95% confidence interval, 0.77-1.15) after controlling for design features (such as dose or use of parallel groups) that tended to be associated with less frequent finding of adverse effects and were more common in PF studies. Among studies finding a statistically significant increase in adverse effects associated with the study drug, the authors of PF articles concluded that the drug was “safe” more frequently than the authors of NoPF studies (prevalence ratio, 3.68; 95% confidence interval, 2.14-6.33).

**Conclusions**: The type of funding may have determinant effects on the design of studies and on the interpretation of findings: funding by the industry is associated with design features less likely to lead to finding statistically significant adverse effects and with a more favorable clinical interpretation of such findings. Disclosure of conflicts of interest should be strengthened for a more balanced opinion on the safety of drugs.

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**METHODS**

A MEDLINE search was performed using PubMed to identify studies on ICS (beclomethasone, budesonide, fluticasone, triamcinolone, or others) meeting the following criteria: original articles; English language used; published...
between January 1, 1993, and December 31, 2002; and provided explicit information on the presence or absence of adverse effects, even if the study of these was not explicitly stated as an aim of the article. The lower time limit was chosen because it was around 1993 when the use of ICs began to be generally recommended in milder cases of asthma, especially in children. The exact MEDLINE query is available at http://admin-pophealth.wisc.edu/icsadverseeffects.

Of the 1834 articles initially identified, 1330 were excluded because they did not show original data (10.0%), studied efficacy but gave no data on adverse effects (39.6%), studied patients already taking systemic corticosteroids or ICs at baseline (14.7%), studied corticosteroids administered by nonrespiratory routes (26.3%), or other reasons (9.4%). The remaining 504 articles were abstracted for the present study (a reference list of these can be obtained at http://admin.pophealth.wisc.edu/icsadverseeffects).

Authors, affiliation, funding sources, and acknowledgments were masked before the data were abstracted. The following data on study design were collected before examination of safety reporting: (1) type of study (single center or multicenter and randomized clinical trial or another type of study [parallel or crossover]), (2) study population (number of patients, adults or children; healthy volunteers; and patients with asthma, rhinitis, or other diseases), (3) dosage (number of days of administration and daily dose classified as high, medium, or low, according to the Global Initiative for Asthma), and (4) stated aims (to study the efficacy of the drug, its safety, or both).

Reported adverse effects were classified into the following categories (methods of assessment are listed in parentheses): adverse events labeled as nonspecific clinical adverse effects (medical history and clinical examination), nonspecific laboratory results (blood count and biochemistry, urinalysis, electrocardiogram, and blood pressure), effects on cortisol metabolism (plasma or urinary cortisol level and response to corticotropin), effects on growth (current height, height velocity, growth hormone, and kнемometry), effects on bone metabolism (densitometry, osteocalcin level, and levels of other enzymes and metabolites, such as phosphatases, hydroxyproline metabolites, and type I procollagen carboxypeptide), and other specific effects (skin, ocular, and psychological) not included in the previous categories. This information was collected from the “Methods” section of each article. From the “Results” section, data were gathered about the presence or absence of statistically significant differences for adverse effects of ICs (using the conventional \( P < 0.05 \) criterion), compared with baseline, with placebo, or with another noncorticosteroid drug (depending on the design of studies).

The authors’ interpretation of adverse effects was collected from the abstract or the discussion section and was classified into 3 categories: “no comments,” “absent or unimportant adverse effects” (drug generally described as safe and well tolerated), and “adverse effects need to be considered.” Two investigators (A.M. and A.N.) independently abstracted the previously mentioned data. Discrepancies regarding the classification of authors’ interpretation (6.9%) were reviewed and adjudicated by a third investigator (R.P.).

Based on the article’s affiliations or acknowledgment section, funding source was classified into 2 categories: (1) pharmaceutical manufacturer funding (PF) (ie, total or partial funding by the pharmaceutical manufacturer of the studied drug) \((n = 269)\) and (2) no PF (NoPF) (ie, funding from a nonprofit scientific or government agency \((n = 74)\) or no declared funding \((n = 161)\)). To verify that the latter did not include studies that had failed to report PF, we attempted to contact the corresponding authors of the 161 studies with no declared funding. Among the 74 who responded, 6 (8.1%) reported PF and were included in the PF group; nonresponders were left in the NoPF group. This yielded 275 PF and 229 NoPF studies. There was no clear trend in the proportion of PF studies during the period covered in our analyses (data not shown).

The design characteristics of the PF and NoPF studies were compared using standard statistical tests: \( \chi^2 \) statistics for proportions and the nonparametric Mann-Whitney test for continuous variables because of their skewed distribution. To compare the relative frequency of finding statistically significant results for adverse effects, prevalence ratios (PRs) and 95% confidence intervals (CIs) were calculated using conventional methods. Multivariate-adjusted PRs were obtained using Poisson regression with robust variance, as recommended by Spiegelman and Hertzmark. The finding of statistically significant results for adverse effects was used as the response variable and the variables found significant in the univariate analysis were used as explanatory variables.

The primary statistical analyses focused on the comparison of all PF and NoPF studies. However, in view of the heterogeneity of studies and to examine the internal consistency of the findings, the analyses were replicated using the more homogeneous subset of 172 double-blind, placebo-controlled, clinical trials identified.

All statistical analyses were conducted using the statistical package SAS, version 8 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Descriptive characteristics of PF and NoPF studies are presented in Table 1. Overall, 34.5% of the 275 PF and 65.1% of the 229 NoPF studies found statistically significant differences for adverse effects (PR, 0.53; 95% CI, 0.44-0.64). Among PF studies, the proportion finding significant adverse effects was 26.5% for the 226 studies reporting exclusive funding by the drug manufacturing company and 71.4% for the 49 studies reporting mixed funding (pharmaceutical company and other organization). Among NoPF studies, the proportion finding statistically significant adverse effects was 73.0% for the 74 studies reporting funding by nonprofit organizations and 61.3% for the 155 studies with no declared funding at all.

Compared with NoPF studies, PF studies were more frequently randomized clinical trials; multicentric; more likely to include adults, to study rhinitis, to use a parallel design in prospective comparative studies, to state that their primary objective was studying efficacy, to use lower dosages of the medication, and to have a larger sample size and shorter follow-up times; and less likely to study patients with asthma (Table 1). The PF and NoPF studies also tended to use different methods to investigate adverse effects. The PF studies were more likely to limit the assessment of adverse effects to only nonspecific clinical and/or laboratory data (PR, 2.82; 95% CI, 1.93-4.15) or cortisol metabolism (PR, 1.30; 95% CI, 1.06-1.59) and less likely to assess other specific adverse effects, such as growth (PR, 0.47; 95% CI, 0.30-0.76) or bone metabolism (PR, 0.28; 95% CI, 0.18-0.45).

In stratified analyses (Table 2), PF studies were less likely to find statistically significant results for adverse effects, regardless of the type of methods used and the stated objective. Particularly striking was the difference among studies assessing only nonspecific clinical and/or laboratory results, in which the finding of statistically sig-
significant results for adverse effects was 4 times smaller in PF than in NoPF studies. In analyses stratified according to type of disease (asthma vs other conditions) and dosage, funding remained strongly associated with the finding of statistically significant results for adverse events. There was no association with duration of the studies ($P = .41$).

**Figure 1** shows the differences in the proportion studying and finding selected types of adverse effects according to the study funding. Again, PF studies more frequently investigated general and nonspecific clinical and laboratory data and less often examined growth retardation and bone metabolism. The likelihood of finding statistically significant results for each specific type of adverse effect tended to be lower in PF than in NoPF studies.

**Table 3** shows the variables that were associated with the finding of statistically significant results for adverse effects in univariate analyses; the rest of the variables excluded from the analysis.
examined (including duration of the study) were not associated with frequency of finding adverse effects (data not shown). Eight of these variables remained significant after adjustment for all the other variables: bronchial administration of the drug, studying medium or high doses, the study of cortisol, and the study of growth were positively associated with increased frequency of finding adverse effects; in turn, studying children, studying nonspecific clinical adverse effects, stating efficacy as an aim, and being a randomized clinical trial were inversely associated with the likelihood of finding adverse effects. Compared with the crude PR of 0.53, the multivariate-adjusted PR associated with PF was 0.94 and was statistically nonsignificant (95% CI, 0.77-1.15), suggesting that the difference associated with funding may be mediated by the other variables included in the analysis.

When analyses were restricted to randomized clinical trials (Table 4), the results were similar to those previously described, although the estimates were more statistically unstable because of the limited sample size. As in the overall analyses, PF trials were less likely to state that the only aim of the study was to investigate safety, less likely to use specific adverse effect measures, and less likely to find statistically significant results for adverse effects, and their authors were more likely to conclude that the drug was safe. As in the overall analysis (Table 3),

![Figure 1](https://example.com/figure1.png)

*Figure 1. Percentage of studies assessing different categories of adverse effects and, among those studying each type of adverse effect, percentage finding statistically significant ($P < .05$) results for the adverse effect: nonspecific clinical adverse effects (A), nonspecific laboratory data (B), cortisol metabolism (C), growth (D), and bone metabolism (E). The prevalence ratios (95% confidence intervals) comparing pharmaceutical manufacturer-funded studies (PFs) with non–pharmaceutical manufacturer–funded studies (NoPFs) are as follows: A, 3.28 (2.53-4.26) for total studies and 0.19 (0.09-0.40) for studies with significant results; B, 5.08 (3.19-8.13) for total studies and 1.70 (0.23-12.35) for studies with significant results; C, 1.30 (1.06-1.59) for total studies and 0.50 (0.38-0.66) for studies with significant results; D, 0.47 (0.30-0.75) for total studies and 0.93 (0.57-1.52) for studies with significant results; and E, 0.28 (0.18-0.45) for total studies and 0.76 (0.45-1.27) for studies with significant results.*


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type of funding became nonsignificant in the multivariate analysis after controlling for other variables associated with funding, such as study of cortisol, study of growth, and using mainly parallel groups (data not shown).

Finally, as presented in Figure 2 and Table 4, the authors of PF studies were more likely than the authors of NoPF studies to conclude that the drug was safe. The difference was particularly striking (PR, 3.68) among studies that did find a statistically significant increase in adverse effects. This difference was even more striking in analysis restricted to randomized clinical trials (PR, 3.91), although, because of the smaller samples size, the corresponding 95% CI slightly overlapped 1 (Table 4).

### Table 3. Crude and Multivariate Associations Between Study Characteristics and the Reporting of Statistically Significant Results for Adverse Effects for All 504 Studies

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Crude Data PR (95% CI)</th>
<th>Adjusted Data PR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmaceutical funding (yes vs no)</td>
<td>0.53 (0.44-0.64)</td>
<td>0.94 (0.77-1.15)</td>
</tr>
<tr>
<td>Studying beclomethasone (vs other corticosteroids)</td>
<td>1.29 (1.08-1.55)</td>
<td>1.05 (0.87-1.26)</td>
</tr>
<tr>
<td>Bronchial administration (vs intranasal)</td>
<td>3.31 (2.20-4.98)</td>
<td>2.38 (1.08-5.24)</td>
</tr>
<tr>
<td>Medium or high daily dose (vs low dose)</td>
<td>3.29 (2.33-4.65)</td>
<td>1.70 (1.20-2.41)</td>
</tr>
<tr>
<td>Studying children</td>
<td>0.73 (0.60-0.89)</td>
<td>0.77 (0.60-0.98)</td>
</tr>
<tr>
<td>Studying healthy adults</td>
<td>1.96 (1.68-2.28)</td>
<td>0.92 (0.63-1.34)</td>
</tr>
<tr>
<td>Studying patients with asthma</td>
<td>1.26 (1.04-1.53)</td>
<td>0.72 (0.50-1.03)</td>
</tr>
<tr>
<td>Studying patients with rhinitis</td>
<td>0.34 (0.23-0.51)</td>
<td>0.95 (0.47-1.91)</td>
</tr>
<tr>
<td>Studying cortisol</td>
<td>1.56 (1.30-1.87)</td>
<td>1.47 (1.22-1.77)</td>
</tr>
<tr>
<td>Studying growth</td>
<td>1.35 (1.09-1.66)</td>
<td>1.41 (1.04-1.92)</td>
</tr>
<tr>
<td>Studying beclomethasone metabolism</td>
<td>1.60 (1.34-1.91)</td>
<td>1.11 (0.90-1.36)</td>
</tr>
<tr>
<td>Studying nonspecific clinical adverse effects</td>
<td>0.38 (0.31-0.48)</td>
<td>0.70 (0.53-0.93)</td>
</tr>
<tr>
<td>Studying nonspecific laboratory results</td>
<td>0.61 (0.47-0.80)</td>
<td>1.24 (0.92-1.66)</td>
</tr>
<tr>
<td>Stating efficacy as an aim (yes vs no)</td>
<td>0.35 (0.28-0.45)</td>
<td>0.68 (0.51-0.90)</td>
</tr>
<tr>
<td>Stating safety as an aim (yes vs no)</td>
<td>1.52 (1.11-2.08)</td>
<td>1.03 (0.78-1.36)</td>
</tr>
<tr>
<td>Randomized study (yes vs no)</td>
<td>0.59 (0.50-0.70)</td>
<td>0.92 (0.74-1.13)</td>
</tr>
<tr>
<td>Multicenter study (yes vs no)</td>
<td>0.41 (0.31-0.54)</td>
<td>0.92 (0.70-1.22)</td>
</tr>
<tr>
<td>Randomized clinical trial (yes vs no)</td>
<td>0.51 (0.40-0.65)</td>
<td>0.73 (0.57-0.93)</td>
</tr>
</tbody>
</table>

Abbreviations: See Table 2.  
\( ^{a} \) Reporting adverse effects with \( P < 0.05 \).  
\( ^{b} \) Data adjusted for all other characteristics in the column.  
\( ^{c} \) Variables with both crude and adjusted significance (\( P < 0.05 \)).

### Table 4. Data for the Presence of a Specific Objective, Study Design, Findings, and Conclusions in 132 PF vs 40 NoPF Double-blind, Placebo-Controlled, Randomized, Clinical Trials

<table>
<thead>
<tr>
<th>Variable</th>
<th>Crude Data PR (95% CI)</th>
<th>Adjusted Data PR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective</td>
<td>1.77 (1.24-2.52)</td>
<td>0.94 (0.79-1.11)</td>
</tr>
<tr>
<td>Stating safety as an aim</td>
<td>0.33 (0.21-0.52)</td>
<td></td>
</tr>
<tr>
<td>Design</td>
<td>4.10 (1.58-10.6)</td>
<td></td>
</tr>
<tr>
<td>Parallel (vs crossover) design</td>
<td>1.73 (1.28-2.34)</td>
<td></td>
</tr>
<tr>
<td>Use of high or medium doses</td>
<td>0.59 (0.47-0.76)</td>
<td></td>
</tr>
<tr>
<td>Assessing only nonspecific clinical or laboratory results</td>
<td>0.61 (0.53-0.81)</td>
<td></td>
</tr>
<tr>
<td>Assessing specific adverse effects</td>
<td>0.40 (0.26-0.61)</td>
<td>0.91 (0.61-1.35)</td>
</tr>
<tr>
<td>Concluding that the drug is safe</td>
<td>1.76 (1.25-2.48)</td>
<td></td>
</tr>
<tr>
<td>All trials</td>
<td>3.91 (0.98-15.6)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: See Table 2.  
\( ^{a} \) Measures of cortisol metabolism, growth retardation, and/or bone metabolism.  
\( ^{b} \) Adjusted for all characteristics given in Table 3.

Our study focused on the statistical rather than on the clinical significance of adverse effects because we were concerned about patterns of differential reporting according to type of funding. \( P < 0.05 \) to define statistical significance is an arbitrary criterion, often inappropriately used as a rigid cutoff to define the presence of associations regardless of their strength or clinical importance.\( ^{21} \) We adopted this criterion, however, to standardize the analysis across a variety of adverse effect outcomes and study designs in the different studies. Because this is the criterion conventionally used to decide on the existence of statistical significance by many researchers, it served as an objective rule to define groups of PF and NoPF studies that, while comparable in terms of the “significance” of the findings, differed with regard to their interpretation. Remarkably, type of funding was a major determinant of the authors’ interpretation of the adverse effects (Figure 2). Authors of PF studies who had

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**Consistent with patterns of studies of other drugs,**\( ^{9,10,13,14,19,20} \) we found that PF studies were less likely to find statistically significant results for adverse effects of ICs. This difference was seen in analyses including all studies, in analyses stratified according to the reported study objective and methods, and in analyses restricted to randomized clinical trials. In addition to funding, significant adverse effects were also associated with a number of study design features, including dose, stated aims of the study, and the type of assessment methods (Table 3). The association between funding and finding adverse effects disappeared in multivariate analyses that controlled for study design variables. This suggests that these differences in design are part of the mechanism explaining the association (ie, they are part of the reason why the frequency of finding adverse effects varies according to the funding source). The alternative explanation (ie, the association between funding and finding of adverse effects is because of confounding) is untenable because for the design features to act as confounders, they would have to be causally associated with funding and not the other way around.\( ^{17} \)
found statistically significant results were less likely to conclude that these were clinically important than their NoPF counterparts. Because they could not be analyzed, we excluded articles on ICs that did not provide data on adverse effects; they accounted for 39.6% (a third of which were PFs) of the excluded studies, a figure astonishingly high considering that this represents omitting data on the safety of a therapeutic intervention. We did include all articles that reported on adverse effects, even those that did not state their assessment as their aim. Most of these were PFs, primarily focused on efficacy (eg, studies conducted to meet requirements for drug approval). Their methods to assess safety tended to be less specific and, not surprisingly, resulted in less frequent finding of statistically significant adverse effects. Studies focusing only on safety were significantly more likely to find adverse effects than studies that also studied efficacy, for PFs and NoPFs. Studies focusing on adverse effects frequently use more sensitive methods and if they find adverse effects, they are more likely to be published than those with negative results. This might result in publication bias, possibly leading to an overrepresentation of studies with harmful effects in the published literature. These results, together with the many studies that gave no information on safety, further support calls for the systematic reporting of adverse effects in current standards for the publication of results of clinical trials and of observational studies of therapeutic interventions.

The definition of “funding source” was based on the authors’ own report. Nevertheless, an unknown number of NoPF studies may have failed to report a PF funding source. In fact, we found that 8.1% of the authors of NoPF studies who had not stated funding source and responded to our inquiry did have PFs. We reallocated these studies in the PF group, but an unknown additional number of studies among the nonresponders might have been misclassified as NoPFs. Among the remainder, those more likely to be truly NoPFs (those reporting funding by nonprofit organizations) had a slightly higher frequency of finding significant adverse effects than those with no reported funding (73.0% vs 61.3%). The fact that the latter is closer to that of PF studies (34.5%) suggests that the resulting misclassification might have biased our results toward the null; had studies been correctly classified, the difference in finding of adverse effects would have been even larger than that reported herein.

Previous reports have shown an association between funding by drug manufacturers and the support of new vs traditional therapies, the safety of calcium channel antagonists, the reduced frequency of adverse effects of nonsteroidal anti-inflammatory drugs, or the better profile in economic studies of oncologic treatments. Our present results seemed to be in line with these reports, but significance faded away after adjusting for other factors. These were design features that are chosen before a study begins, that were significantly different in PF and NoPF studies, and that seem to have a determinant effect on the outcome.

The interpretation by authors of their own findings greatly differed between PF and NoPF studies. The extrapolation of statistical to clinical significance is based on subjective criteria, so we cannot estimate if PF studies are too benevolent or NoPF studies are too cautious.

![Figure 2. Percentage of studies that find any statistically significant results for adverse effects, that conclude the drug is safe among all studies, that conclude the drug is safe among those that did not find significant results for adverse effects, and that conclude the drug is safe among those that found some significant results for adverse effects. The prevalence ratios (95% confidence intervals) of pharmaceutical manufacturer-funded (PF) compared with non–pharmaceutical manufacturer-funded (NoPF) studies are as follows: 0.53 (0.44-0.64), 2.10 (1.73-2.54), 1.10 (1.00-1.20), and 3.68 (2.14-6.33), respectively.](image-url)
However, we postulate that having information on source of funding will help readers of these studies have a better informed and balanced judgment on the authors’ interpretations. Because the abstract is often the only section available to clinicians without access to well-supplied medical libraries, we suggest that it might be desirable to require the disclosure of source of funding in the abstract of the article.

In the case of ICs, all these issues are important because their manufacturers fund much of the literature on their clinical use. As a result, systematic reviews or meta-analyses of the literature on this topic, including those conducted by consensus committees, may be based on limited information on their risks and benefits. The lack of complete and unbiased evidence on the safety profile of these drugs has an important effect on clinical practice because safety is one of the multiple factors influencing physicians’ treatment decisions. While benefits outweigh the risks in severe asthma cases, this may not be the case in milder cases. We focused on ICs, but results probably will be applicable to many other drugs and therapeutic interventions. Therefore, emphasizing the importance of evidence-based therapeutic recommendations will be of little use if the available evidence is biased in any direction.

In summary, our findings support maintaining or even strengthening medical journals’ full disclosure policies regarding funding source. In addition, the introduction of a new conflict of interest field in the MEDLINE database (that could be searched and displayed like all the other fields) should also be considered.}

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REFERENCES


