

**Konstanty Radziwiłł<sup>1</sup>, Jerzy Kruszewski<sup>2</sup>**

<sup>1</sup>Family Medicine Outpatient Clinic, Warsaw

Head: K. Radziwiłł MD PhD

<sup>2</sup>Department of Infectious Diseases and Allergology, Central Hospital of the Ministry of National Defence, Military Medical Institute, Warsaw

Head: Prof. J. Kruszewski MD PhD

## Evaluation of placebo effect in treatment of asthma based on metaanalysis of trials on selected antiasthmatic drugs

### Ocena wielkości efektu placebo w leczeniu astmy na podstawie metaanalizy badań skuteczności wybranych leków przeciwastmatycznych

At the time of paper preparation, Dr. Radziwiłł was employed at the Military Medical Institute.

#### Abstract

**Introduction:** Apart from the well-studied mechanisms of disease course modification, many therapeutic interventions, at least in part, exert non-specific effects on patients. These effects can be measured by patient self-assessment or by technical analyses. The aim of the study was to assess the extent of placebo effect in the treatment of asthma based on reevaluation of results of high-quality trials on inhaled antiasthmatic drugs and in the context of various applied investigative methods.

**Material and methods:** A systematic search of the Medline database (using the Entrez Pubmed browser) was performed using international drug names and English terms: inhaled, randomised, placebo-controlled. The aim of the search was to identify trials on the efficacy of inhaled antiasthmatic drugs. Of the returned 454 studies, 41 were further included in metaanalysis and assessed for correlations between drug effects and respective applied investigative methods. For comparison, analogical analysis was performed for captopril, with 232 identified published studies of which 10 were included in the metaanalysis.

**Results:** The placebo effect in the treatment of asthma was significantly stronger (29%) as compared to the placebo effect of captopril in patients treated for arterial hypertension (17%). The placebo effect was more prominent in studies applying clinical (subjective) indicators of drug efficacy as compared to trials using objective (device-based) methods of drug effect measurement.

**Conclusions:** The placebo effect is more prominent in treatment of asthma as compared to pharmacotherapy of arterial hypertension. Its extent depends on the applied methods of drug efficacy measurement and is often greater if only clinical indicators are used. This phenomenon can lead to different interpretations of treatment goals in asthma as perceived by the physician and the patient. This also points out the necessity of patient activation in taking control over his/her disease so as to achieve a better and more satisfying treatment result.

**Key words:** asthma, placebo effect, meta-analysis

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#### Introduction

The efficacy of therapeutic interventions does not only rely on their potential to modify the course of the disease, as best exemplified by pharmaco-

logical therapy, where the specific drug effect is not the exclusive curative mechanism involved [1–3].

Contemporary treatment of asthma is aimed at controlling the course of the disease using various inhaled agents having different mechanisms

**Address for correspondence:** Konstanty Radziwiłł MD, ul. Mielczarskiego 1, 02–798 Warszawa, tel./fax: +48 (22) 648 49 56, e-mail: k.radziwill@hipokrates.org

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of action. These include mainly anti-inflammatory drugs (glycocorticosteroids) and bronchodilators (beta-agonists) [4]. Similarly to other chronic diseases, there is also a “milieu” effect of the involved in therapy of asthma. Referred to as the placebo effect, this phenomenon can at times be strong enough to become a significant element of the therapeutic process, apart from the well-defined actions of the applied antiasthmatic pharmacologic agents. The particularities of the placebo effect may have some explanation in yet unknown pathophysiological mechanisms of allergic reactions underlying asthma, interactions between the immune system and the nervous system (including the patient’s psyche) or the characteristics of the disease, with its episodic appearance of symptoms. This may lead to specific patient preferences as to the choice of particular agents. Antiasthmatic drugs are tested and evaluated during numerous pre- and postregistration trials, where their effects are compared to placebo. However, there are no analyses concerning the proportion of drug effect and placebo effect in the overall treatment result in asthma.

The aim of the current study was to evaluate the placebo effect in the treatment of asthma based on the results of previously published high quality trials concerning inhaled antiasthmatic agents. Moreover, the extent of the placebo effect in the therapy of asthma was also evaluated with respect to various applied investigative methods.

## Material and methods

### Material

A systematic search of the Medline database (using the Entrez Pubmed browser) was performed in order to identify randomized placebo-controlled (most often double-blinded) trials concerning inhaled antiasthmatic drugs and (for comparison) antihypertensive agents.

The following antiasthmatic agents were included in the analysis:

- a) beclomethasone, fluticasone,
- b) formoterol.

The following antihypertensive agent was also analysed for comparison:

- c) captopril.

Search terms included: international drug name in English (beclomethasone, fluticasone, formoterol, captopril) and the words: inhaled (for antiasthmatic agents), randomised, placebo controlled.

Table 1 presents the results of a literature search for particular pharmacologic agents as the first step of the analysis. An initial verification procedure was performed so as to exclude browser-related errors. The trials included in the final analysis fulfilled the following criteria:

- a) trial concerned only asthma or only arterial hypertension (for captopril);
- b) results of trial were published in a peer-reviewed journal;
- c) of all the patients who completed the trial, the number of persons receiving an active pharmacologic agent (study group) was similar to the control group receiving placebo, with an intergroup difference of not more than 5%;
- d) inclusion criteria were clearly defined, and indicators of treatment were efficacy well established, including both the objectively measurable effects (e.g. FEV<sub>1</sub> or PEF as objective markers of bronchial hyperreactivity) and subjective estimators, including parameters assessed by patients themselves or by investigators (various scales of disease intensity, amount of drugs consumed, quality of life measurement). Study duration, endpoints, and final results had to be clearly presented and available in the publication main text or abstract for further re-evaluation.

### Statistical analysis

All statistical analyses were performed with kind assistance from Prof. Mieczysław Kłopotek Dr. Ing. (Institute of Computer Sciences, Polish Academy of Sciences) and Maciej Michalewicz Dr. Ing.

**Table 1. Stages of a systematic review of the studies eligible for analysis**

Agent	Trials identified n	Trials after initial verification n (%)	Qualified for analysis n (%)
Beclomethasone	111	95 (86)	10 (11)
Fluticasone	210	170 (81)	29 (17)
Formoterol	133	110 (83)	2 (2)
Captopril	232	192 (83)	10 (5)
Total	686	567 (83)	51 (7)

(IBM Poland). Three variables were analysed for each trial, when possible:

- a) effect of treatment reflecting changes in the measured parameter in the study group (EL);
- b) placebo effect reflecting changes in the measured parameter in the placebo group (EP);
- c) placebo effect to treatment effect ratio, reflecting proportion of the final treatment effect that can be contributed to placebo effect (UEPL).

For some studies, the first two variables could not be analysed. Analysis was feasible if:

- a) changes in the measured parameter were of incremental or decremental character, with known or obvious maximal (or minimal) value or established reference range;
- b) changes in the measured parameter were of incremental or decremental character, and its maximal (or minimal) value or reference range could be predicted (hypothesized).

At times, the measured parameters and their characters precluded calculation of the EP and LP values but UEPL could still be calculated; the latter was then accepted as the final analysis result.

When measured parameters were expressed in percentage values, analysis was based on arithmetic mean values of the percentage of patients in the study group and in the control group using Bernoulli distribution, with the assumption that both patient groups were equal in size. Significant correlations were assigned when probability was of more than 0.95 or less than 0.05.

For trial results expressed as numeric values, differences in arithmetic mean values were tested for statistical significance between the study group and the control group using Student's *t* test, with the assumption that both groups were equal in size. For some parameters, mean values and standard deviation were calculated:

- a) based on analogical studies, if significance level was given, or
- b) assuming that standard deviation value does not exceed mean value, or
- c) assuming that standard deviation value is known to the investigator from other sources.

If standard deviation (SD) from the mean value was not given, reversed *t* test was used to determine SD based on the *p*-value from another literature reference. When using Student's *t* test, an adequate number of degrees of freedom was assumed, taking into account the number of patients in the study group and the control group. Corrected standard deviation for a single trial was also estimated.

Various parameters are used in trials concerning different diseases. These are, however, extremely heterogeneous and difficult to summarize;

therefore, the study group was replaced by a "metapatient" for the sake of metaanalysis, and respective parameters were replaced by the notions of EL in relation to EP. Consistency of respective trial results was verified, being the main selection criterion for further analysis.

## Calculations

Mean values for all the analysed parameters (both clinical and objective ones) as well as EL, EP, and UEPL for the four drugs in question were calculated. The following drug combinations were also investigated in the same manner:

- a) beclomethasone and fluticasone;
  - b) beclomethasone, fluticasone, and formoterol.
- Analogical calculations were also performed for:
- a) trials using clinical parameters (through "objectivisation" of anamnestic data);
  - b) trials using objective parameters (using given measurement results).

Next step involved comparison of mean values for respective drugs, combinations of drugs (antiasthmatic agents and captopril) and for treatment of asthma and hypertension (the latter therapy involving captopril). Calculation results were presented graphically and in tables, giving mean values and *p* values for differences between the analysed groups.

## Results

Clinical efficacy of the studied drugs versus efficacy of placebo

Cumulative results of calculations based on subjective and objective parameter values for antiasthmatic agents are presented in figure 1.

The two analysed inhaled glyocorticosteroids had different efficacy. Fluticasone caused improvement of 68%, and beclomethasone 49%, but EP for fluticasone was almost 1.5 times better. The effect of beclomethasone therapy was greater than EP (2.9 times) and exceeded the effect of fluticasone (2.5 times the effect of placebo); the difference was not statistically significant, though.

Formoterol had a weaker effect as compared to other agents (17% EL). Placebo effect for this drug was also weaker (4%). The effect of the drug significantly exceeded its EP (by 4.9 times).

Captopril had a 44% EL, with low EP effect of 9% on average. The effect of the drug exceeded the placebo effect by 5 times.

The greatest difference between EL and EP was observed for captopril (5.0) and formoterol (4.9), with a statistically significant difference ( $p > 0.001$ ) between these agents and inhaled glyocorticoste-

roids (with respective values of 2.9 for beclomethasone and 2.5 for fluticasone).

Cumulative EL of antiasthmatic drugs (beclomethasone, fluticasone, and formoterol) in the cited trials was 54%. Control groups receiving placebo had a significantly weaker effect of 23% ( $p < 0.001$ ). Summaric EL effect of antiasthmatic agents exceeded EP by 1.9 times, and thus was significantly less than that of captopril ( $p < 0.001$ ).

### Comparison of different methods of treatment effect measurement

Analysis concerning various methods of treatment efficacy assessment revealed that the placebo effect was significantly stronger ( $p < 0.001$ ) when clinical indicators of efficacy were employed (mean effect of 59%) as compared to studies using objective measurements (mean effect of 29%).

### Contribution of drugs and placebo to the overall treatment effect

Figure 2 depicts the contribution of respective pharmacological agents and placebo to the overall treatment effect measured using both clinical and objective indicators. The weakest placebo effect was observed in trials concerning captopril, whereas among antiasthmatic agents the least effective was shown to be formoterol, followed by beclomethasone and fluticasone.

## Discussion

The presented analysis demonstrates that the placebo effect plays an important role in the treat-

ment of asthma. This observation concerns all the three analysed inhaled antiasthmatic agents, with placebo effect greater than that of an antihypertensive agent. The finding may imply that asthmatic patients are more prone to placebo effect and benefit from it to a larger extent than patients with hypertension. The role of psychosomatic phenomena in asthma can therefore be hypothesized, which reflects a growing field of scientific interest [5–10].

The coincidence of asthma with anxiety and depressive disorders is well known. Some authors and doctrines suggest the necessity of addressing these issues in order to improve results of asthma therapy [4, 11]. The patient's feeling of having greater control of the disease and increased safety may decrease the intensity of asthmatic symptoms to a greater extent as compared to other ailments. Current recommendations concerning the treatment of asthma emphasise the necessity of stress reduction in patients [4]. Greater patient engagement in disease monitoring and decision-making concerning administration of fast acting medication is suggested.

The presented analysis demonstrates that methods (objective versus subjective) and conditions of therapeutic efficacy assessment are crucial for evaluation of the placebo effect. Clinical parameters are more widely used in recent trials, given their simplicity, low cost, non-invasive character, and possibility of quick assessment, although subjective character and lack of accuracy are still admitted in these settings. The current analysis confirmed that the more subjective measurement techniques applied in asthma treatment, the less precise the results. These are, however, closer

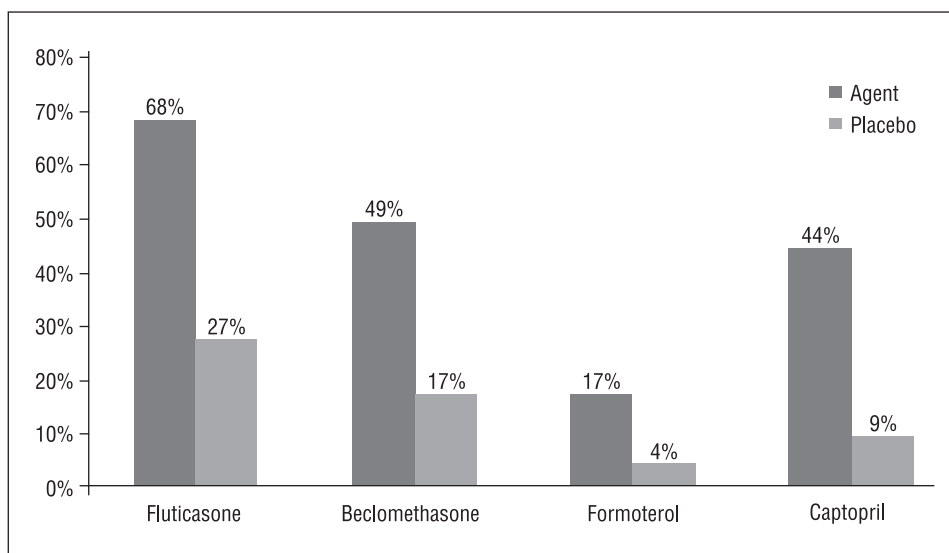


Figure 1. Average EL and EP levels in placebo-controlled trials of efficacy of antiasthmatic inhaled drugs evaluated by objective and subjective indicators

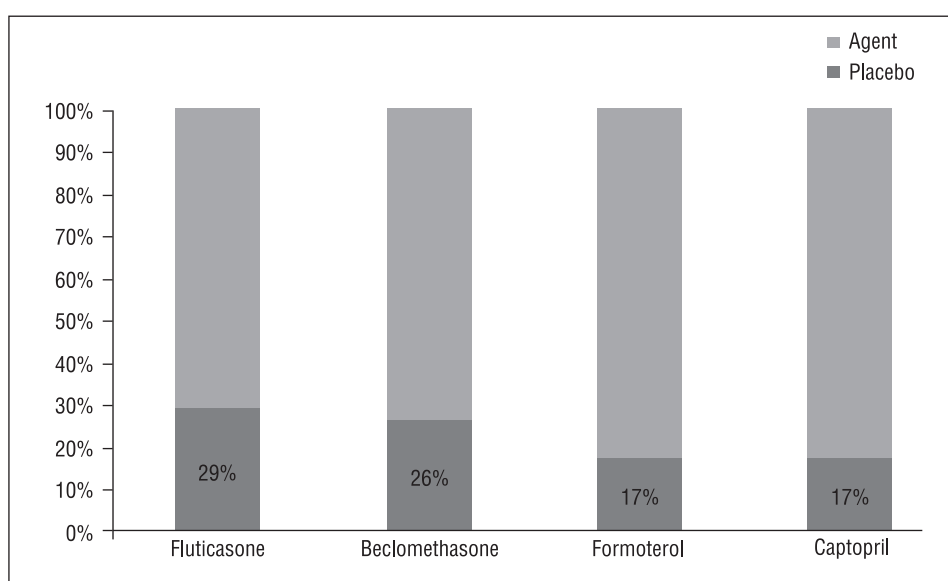
to the patient's perception of the disease course and treatment effect. The presented results also demonstrate that the more subjective evaluation methods applied, the greater the extent of the placebo effect in the cumulative result of treatment.

To assess if a given therapeutic intervention (drug) has a real impact on a disease course, a study group in a clinical trial is observed to find out if these individuals experience a greater treatment effect than subjects in a control group who receive placebo. In the latter group, however, there is also the influence of natural, non-drug-dependent tendencies for convalescence. This approach is correct, given that the intervention (drug) is most often developed based on rational knowledge of the disease, and the question to be answered is whether this intervention can have a beneficial effect on the given disease. Efficacy of the intervention is therefore perceived as its effect on the already known disease-causing mechanisms. Physicians intend to use medication of known and proven efficacy but they actually observe and measure the cumulative effect of treatment. This may mean that a beneficial effect can be also obtained if other agents or interventions, with no perceptible effect on the disease, are applied. Many well-established drugs, including antiasthmatic agents, undergo negative verification with time. Comparing their therapeutic effects with those of the placebo can prove that interventions with no real influence on the disease course can be erroneously perceived as beneficial [12-14]. The presented results show that such errors can occur in daily practice, and physicians

are not able, even approximately, to estimate proportional contributions of different interventions to the overall therapeutic effect. In addition, physicians tend to underestimate the placebo effect, which is a reason for the success of many alternative medical interventions and strategies.

The UEPL ratio adopted in this study is easy to calculate using the available data and reflects the proportions between a real therapeutic effect of the drug and that of the placebo. Using it permits clear definition of both proportions, which can be useful in daily practice but also making comparisons and analyses giving a greater insight into the placebo effect.

It is well known that the disease and its treatment have impact on the patient's perception of his/her environment and effects of therapy but can also influence the degree of the experienced placebo effect, and asthma is a good example of this. Numerous studies emphasise specific psychical features of affected patients, some of them of almost borderline character, which may predispose them to a greater benefit from the placebo effect. The presented study confirms these theories, demonstrating that patients with asthma can experience a particularly strong placebo effect if treatment outcomes are measured by clinical indicators and scales. Of note, the placebo effect varied between different trials concerning the same drug, which warrants greater attention to the interpretation of published results, even in cases of properly constructed and formally immaculate trials on antiasthmatic drugs.



**Figure 2.** Average share of placebo in a total effect of treatment in in placebo-controlled trials of efficacy of antiasthmatic inhaled drugs evaluated by objective and subjective indicators

### Conclusions

1. Contribution of the placebo effect in high-quality clinical trials on inhaled antiasthmatic drugs was variegated but significantly greater as compared to studies on an antihypertensive agent, captopril.
2. Greater placebo effect was observed in trials where the therapeutic effects were measured using subjective (clinical) indicators as compared to analyses based on more subjective assessments (device-based readings and measurements).

### Conflict of interests

The authors declare that no conflict of interests occurred during the process of the paper preparation.

### References

1. Bogdanik T. Współczesne poglądy na placebo. *Przegl. Lek.* 1996; 53: 481-485.
2. Danysz A., Buczek W. *Kompendium farmakologii i farmakoterapii.* Urban & Partner, Wrocław 2008.
3. Kleijnen J., de Craen A.J., van Everdingen J., Krol L. Placebo effect in double-blind clinical trials: a review of interaction with medication. *Lancet* 1994; 344: 1347-1349.
4. [www.ginastma.org](http://www.ginastma.org).
5. Howland R.H. Understanding the placebo effect. Part 2: underlying psychological and neurobiological processes. *J. Psychosoc. Nurs. Ment. Health Serv.* 2008; 46: 15-18.
6. Czubalski K. Czynniki psychiczne w działaniu leków. *Sztuka Leczenia* 1995; 1: 53-61.
7. Göttsche P.C. Is there logic in the placebo? *Lancet* 1994; 344: 925-926.
8. Zimbardo P.G., Ruch F.L. *Psychologia i życie.* PWN, Warszawa 1988.
9. Brady J. (red.). *Psychiatria.* Spectrum, New York 1977.
10. Kemeny M.E., Rosenwasser L.J., Panettieri R.A., Rose R.M., Berg-Smith S.M., Kline J.N. Placebo response in asthma: a robust and objective phenomenon. *J. Allergy Clin. Immunol.* 2007; 119: 1375-1381.
11. Zalewska-Janowska A. *Psychodermatologia w alergologii.* *Alergia Astma Immunol.* 2010; 15: 109-117.
12. Shang A., Huwiler-Müntener K., Nartey L. et al. Are the clinical effects of homeopathy placebo effects? Comparative study of placebo-controlled trials of homeopathy and allopathy. *Lancet* 2005; 366: 726-732.
13. Kruszewski J. *Metody medycyny alternatywnej w chorobach dróg oddechowych.* W: Ligęziński A., Jurkiewicz J. (red.). *Postępy w rozpoznawaniu i leczeniu chorób górnych dróg oddechowych o podłożu immunologicznym.* Urban & Partner, Wrocław 1999; 338-369.
14. Pietras T., Panek M., Witusik A. et al. Analiza zależności pomiędzy łękiem, depresją i nasileniem duszności a ciężkością przebiegu astmy oskrzelowej. *Post. Dermatol. Alergol.* 2010; 27: 390-399.