Evaluation of the size of the placebo effect in treatments of allergic diseases and asthma based on a meta-analysis of efficacy trials of drugs

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Abstract

Introduction: Many methods of treatment use at least partially not only their influence on the disease mechanism but also their non-specific effects. The non-specific result of a therapy is stronger when there are more psychogenic factors in a given disease. It can be measured using both objective and subjective indicators. Many special features of allergic diseases suggest that a placebo effect may be an important factor of a total result obtained during their treatment. It also appears that a placebo effect is stronger when measurements of the effectiveness of the treatment are subjective.

Material and methods: After a systematic review of the Medline database and meta-analysis of publications of results of randomized placebo-controlled efficacy trials of drugs used to treat allergic diseases and asthma (755 publications concerning 22 457 patients), and investigation of its dependence on the type of diseases and indicators used, it has been demonstrated that a placebo effect in treatments of these diseases was significantly higher (up to 40%) than in the treatment of hypertension with captopril (17%) (232 publications concerning 2 732 patients).

Results: It was found that placebo had the highest share in a therapeutic effect in allergic rhinitis (57%), which differs considerably from the case of asthma (34%) and allergic skin diseases (32%). The share of the placebo effect was also significantly higher in studies in which clinical (subjective) indicators were used (59%) compared with studies using objective indicators of drug efficacy (29%).

Key words: allergic diseases, placebo effect, meta-analysis.

Introduction

It is widely known that the effectiveness of treatment methods depends not only on their impact on the course of the disease. A good example may be pharmacotherapy, effects of which depend not only on specific (pharmacological) action of the administered drugs [1-3]. It is suggested that because of still unexplored compounds, mechanisms of allergic and immunological reactions and functions of the nervous system (psyche) in treatments of allergic diseases and the aura (atmosphere) accompanying treatment may be especially pronounced, making the placebo effect an important factor in the effect of summary results obtained by the application of objective methods affecting the mechanisms of allergic diseases.

Aim

The aim of this study was to assess the size of the placebo effect in treatments of allergic diseases and asthma based on an analysis of already published high quality trials of the efficacy of drugs used in treatment of allergic diseases and asthma and to investigate its dependence on the type of disease and the drug effectiveness measures used.

Material and methods

Material

A systematic review of the Medline publications database was made using EntrezPubmed search engine to

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find high quality publications of placebo-controlled drugs used to treat allergic rhinitis (AR), asthma (A) and allergic skin diseases (ASD) and hypertension efficacy trials.

The following drugs were included in the analysis: antihistamines – cetirizine, fexofenadine and loratadine; inhaled glucocorticosteroids – beclomethasone and fluticasone; inhaled long-acting β_2-mimetic – formoterol; and captopril used in hypertension.

Search criteria included the international drug name in English, and the words *randomized*, *placebo*, and *controlled*.

Table 1 shows the number of first-found publications concerning specific drugs. The first selection was of a technical nature and concerned elimination of technical errors of the search. The studies ultimately included in the analysis had to fulfil the following conditions:

a) results of a trial must be published in a peer-reviewed journal,
b) the actively treated group and placebo group must be of a similar number,
c) there must be a precise definition of inclusion in the trial, metrics, evaluation of efficacy, duration and endpoint of the study,
d) presentation of results should be in a form allowing a reliable assessment of the drug and placebo,
e) calculation of the necessary indexes must be available in the summary.

The assessment of the literature showed that the authors of individual studies used very different parameters of effectiveness. The diversity of indicators was so large that it was difficult to harmonize them. Hence, a substitution of abstraction of a group of patients by a "meta-patient" and various indicators by a general concept to refer treatment effect (TR) to placebo effect (PR) was done. Consistency of the results of individual studies presented in the literature was verified; it constituted one of the basic eligibility criteria for the selection of studies for further analysis.

Methods

Methodological assumptions were developed and all the calculations were done in collaboration with Mieczyslaw Klopotek (Institute of Computer Science, Polish Academy of Sciences) and Maciej Michalewicz (Netezza Poland Ltd.). For each survey, if possible, three parameters were calculated:

a) TR index reflecting changes of the improvement indicator value in a group receiving the drug,
b) PR index reflecting changes of the improvement indicator value in a group receiving placebo,
c) ratio of placebo effect to effect of treatment (SPRT), a value which reflects the proportion of the placebo effect in the total treatment effect.

Calculation of the first two indexes was not always possible. Situations in which they can be counted occurred when:

a) an indicator used in a test was of increasing or decreasing character with a known or obvious maximum (minimum) or norm,
b) an indicator was of increasing or decreasing character, and one could assume the maximum (minimum) or the range of norm.

When it was not possible to calculate TR and PR indexes, and it was possible to calculate the SPRT index, only it's value was analyzed.

In studies using percentage indicators, the evaluation of the significance of differences of arithmetic means of percentages of patients in active treatment and placebo (assuming that the placebo and active treatment groups were of the same number) using the Bernoulli distribution was done. It was assumed that the relationship was significant if the probability value reached a value of more than 0.95 or less than 0.05 ($p < 0.05$).

In group studies with numerical indicators, evaluation of the significance of differences of the arithmetic average values of numerical parameters of patients in active treatment and placebo using Student's *t*-test, also assuming that the placebo and active treatment groups were of the same number, was done. Estimation of the arithmetic mean standard deviation of some of the parameters was done:

a) on the basis of similar studies, when the level of significance was known or
b) by assuming that the standard deviation does not exceed the average or
c) by assuming that the deviation was known to researchers from other sources (similar tests).

In the absence of standard deviation from the mean value, a *t*-test inversion method was used to find this value, based on knowledge of the level of the same parameter in other publications. In calculating the *t*-test statistic, it was assumed a relevant number of degrees of freedom, based on the number of patients in the actively treated and placebo groups and corrected and estimated standard deviation of a single study.

Table 1. Stages of systematic review of studies eligible for analysis

Drug	Found	First review		Qualified	
	n	*n*	%	*n*	%
Cetirizine	104	88	85	44	50
Fexofenadine	79	65	82	7	11
Loratadine	118	100	85	33	33
Beclometasone	111	95	86	10	11
Fluticasone	210	170	81	29	17
Formoterol	133	110	83	2	2
Captopril	232	192	83	10	5
Total	987	820	83	135	16

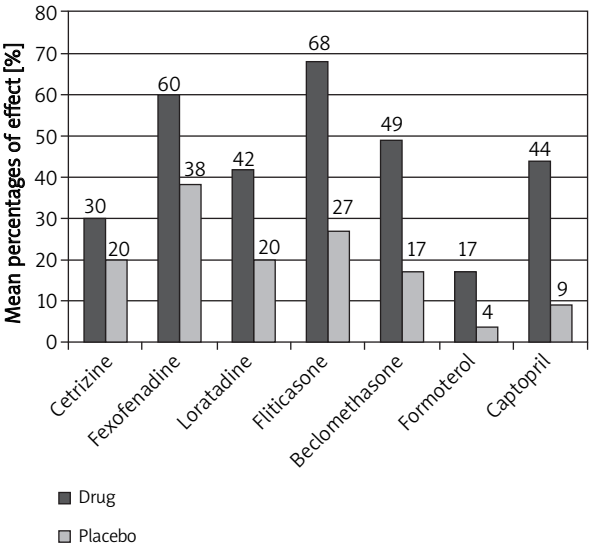

Fig. 1. Mean percentages of drug effect (TR) and placebo effect (PR) in placebo-controlled efficacy and anti-allergic and anti-asthmatic drugs

Calculations

The mean ratios were obtained for all TR, PR and SPRT indexes for all studies of a particular drug, and for comparison, also for selected groups of drugs:

a) cetirizine, fexofenadine and loratadine,
b) beclomethasone and fluticasone,
c) beclomethasone, fluticasone and formoterol,
d) cetirizine, fexofenadine, loratadine, beclomethasone, fluticasone and formoterol.

Similar calculations were done for:

a) trials using subjective (clinical) indicators,
b) studies using objective indicators,
c) studies of allergic diseases: AR, A, ASD and hypertension treated with captopril.

A further step was to compare average ratios for individual drugs, anti-allergic and anti-asthmatic drug group and captopril, as well as for each allergic disease and hypertension treated with captopril using Student's *t*-test. The calculation results are illustrated in figures and tables presenting average values and levels of significance of differences between the distinguished groups.

Results

Clinical efficacy of selected drugs and the effectiveness of the placebo

The results are shown collectively in Fig. 1. As it is clear from Figure, the indicators of effectiveness of the three tested antihistamines differ: cetirizine caused about 30%, fexofenadine 60% and loratadine 42% improvement in the indicators. The PR was nearly two times bigger in the fexofenadine studies than in studies of cetirizine and loratadine. The TR for loratadine to a greater extent surpassed PR (2.1 times) compared with fexofenadine (1.6 times) and cetirizine (1.5 times).

The two tested inhaled glucocorticosteroids also differed in the change of performance indicators. Fluticasone caused almost 68% and beclomethasone 49% improvement. The PR was almost one and a half times greater in the fluticasone studies. The effect of beclomethasone to a greater extent surpassed PR (2.9 times) compared to fluticasone (2.5 times).

Formoterol-caused TR compared with the other drugs was relatively small (only 17%). The PR in these studies was also relatively small and amounted to 3.5%. However, the effect of formoterol in a relatively high degree surpassed PR (4.9 times). Captopril caused a 44% TR, and PR in the studies of the drug was relatively low and amounted only to 8.7%. The drug effect 5 times surpassed the placebo effect.

As is apparent from Table 2, TR surpasses PR to the greatest degree in the case of captopril (5.0), as in the case of formoterol (4.9). The effect of the other drugs, inhaled corticosteroids (beclomethasone – 2.9 and fluticasone – 2.5) and relatively little antihistamines (loratadine – 2.1, fexofenadine – 1.6 and cetirizine – 1.5), exceeded the PR, which differs significantly from captopril ($p < 0.001$) (Table 3).

Anti-asthmatic and anti-allergic drugs resulted in an average of 54% TR in the analysed studies. In the placebo group, this effect was smaller, and stood at an average of 23.0%, which was statistically significant ($p < 0.001$). The TR cumulatively 1.9 times surpassed PR, which differed significantly from the action of captopril ($p < 0.001$).

Comparisons of different types of indicators of drug efficacy

Table 4 presents the SPRT dependence on the type of allergic disease. It was found that SPRT was the highest in the case of AR, averaging 57%. It was significantly higher ($p < 0.001$) than in the case of A and ASD, in which diseases it was respectively 34% and 32%. There were no significant differences when comparing SPRT for A and ASD.

Figure 2 illustrates the part of the action of selected drugs and placebo in the overall therapeutic effect. As is apparent from the figures, the lowest percentage of the placebo effect was observed for captopril. Among the anti-allergic and anti-asthmatic drugs, the effect was the smallest in the case of formoterol and successively beclomethasone, fluticasone, loratadine, fexofenadine and the greatest for cetirizine.

Discussion

The presented analysis authorizes to conclude that the placebo effect is a very important part of the summary

Table 2. Comparison of the significance of differences in the effect of tested drugs and the various classes of drugs (1-3), (4, 5) (4-6) (1-5) with captopril (7)

Drug	1	2	3	4	5	6	7
1. Cetirizine	–	ns	ns	ns	0.04	0.001	0.002
2. Fexofenadine	ns	–	ns	0.04	0.04	0.007	0.005
3. Loratadine	ns	ns	–	0.02	ns	0.001	0.009
4. Beclometasone	ns	0.04	0.02	–	ns	ns	ns
5. Fluticasone	0.04	0.05	ns	ns	–	0.001	0.02
6. Formoterol	0.001	0.007	0.001	ns	0.001	–	ns
7. Captopril	0.002	0.006	0.01	ns	0.02	ns	–
8. 1 + 2 + 3	–	–	–	ns	0.03	0.001	0.002
9. 4 + 5	0.02	0.04	ns	–	–	0.001	0.03
10. 4 + 5 + 6	0.01	0.04	ns	–	–	–	0.03
11. 1 + 2 + 3 + 4 + 5	–	–	–	–	–	–	0.001

p value is given in the table, ns – non-significant

effect of the treatment of allergic diseases and asthma. This was true for all analysed drugs used in these diseases. In their action, part of the placebo effect was significantly greater than that of captopril used for treatment of disease of a different character – hypertension. This indicates that patients with allergic diseases and asthma are more likely than patients with hypertension to be susceptible to the effect of placebo. Therefore they constitute a group particularly sensitive to the placebo effect, which strengthens the belief of a significant share of psychosomatic phenomena in these diseases [4-9].

Well known are compounds of allergic diseases and asthma with anxiety-depression disorders, which in patients with asthma are 2 times more frequent than in the general population. Some authors highlight the need to consider these phenomena, if one wants to improve the outcome of these patients [10]. Increased sense of surveillance, control and confidence can more strongly than for other diseases reduce symptoms of patients with allergic diseases and asthma. Current recommendations for treatment of these diseases emphasize the need to reduce stress in patients [10]. Activities

Table 3. The UEPL in anti-allergic drug studies according to the approved kind of measure of evaluation of drug efficacy

Measure	Arithmetic mean	SD	Level of significance
Objective (device using)	29%	30%	$p < 0.001$
Subjective (clinical)	59%	40%	

Table 4. The UEPL in anti-allergic drug studies depending on the disease

Disease	Arithmetic mean	SD	Level of significance
AR	57%	30%	A – $p < 0.001$, ACS – $p < 0.001$
A	34%	26%	ANN – $p < 0.001$, ACS – ns
ASD	32%	32%	ANN – $p < 0.001$, A – ns

AR – allergic rhinitis, A – asthma, ASD – allergic skin diseases, UEPL – proportion of placebo effect

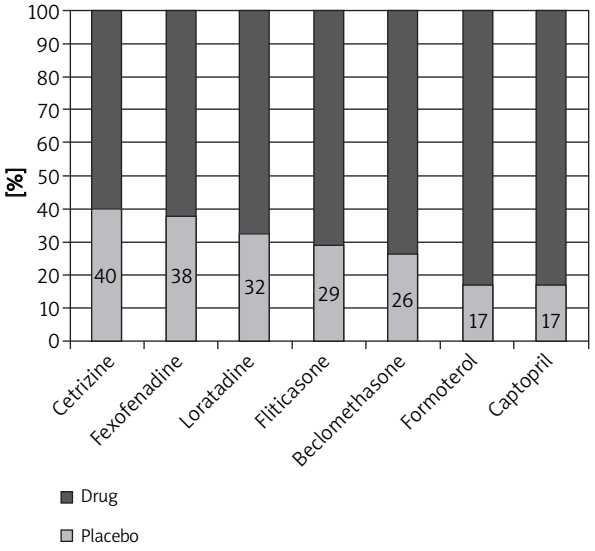

Fig. 2. Mean percentages of the total share of the placebo effect in placebo-controlled therapeutic efficacy studies of anti-allergic and anti-asthmatic drugs

aimed at a greater involvement of the patients in the monitoring of the disease and making decisions about the use of controlling disease and ad hoc drugs are proposed [10]. Such actions affecting the aura (atmosphere) accompanying treatment also enhance the placebo effect.

The share of the placebo effect, although sometimes quite different in single drug studies, as in similar studies with antihistamines also pointed out by other authors, in comparisons with the drugs within the same pharmacological group was similar and not significantly different [11]. There were also no significant differences in comparisons of certain groups of medications such as antihistamines and inhaled corticosteroids. Significant differences involved comparisons between drug groups, as well as all drugs used in allergic diseases and asthma with captopril in hypertension.

Differences in placebo effect between different diseases were also found – the highest in AR and lower in asthma and ASD. Probably due to the fact that various allergic diseases or groups of diseases differ in terms of participation of psychosomatic phenomena in the pathogenesis and the course, for that reason alone, they pose varying degrees of inconvenience in the daily life of patients and are in varying degrees susceptible to treatment [12, 13].

The analysis also showed that the kind of parameter (objective in nature or subjective (clinical)) which had been used in evaluating the effectiveness of treatment and the placebo had a significant impact on the share of the placebo effect. In recent times the advantages of clinical parameters which, although based on many subjective factors and imprecision, are characterized by low cost, simplicity, and the possibility of direct non-destructive and rapid assessment, are being highlighted. The current analysis confirms the view that although the measure of the clinical evaluation of treatment of allergic diseases and asthma is less precise, improving these indicators is closer to the threshold of feeling improvement by a patient. On the other hand, it confirms that the less subjectivity in assessing the effect of the treatment of allergic diseases and asthma, including the participation of the placebo, the smaller effect is observed.

It is known that each person can be influenced by placebo. In order to assess the actual impact of the active treatment of a given disease, these actions are disregarded, and it is examined whether a group treated with an active drug gets better compared to a placebo group, i.e. whether the drug effect is greater than both placebo and the natural tendency to recovery. It is the right approach when it comes to answering the question of how a drug to be used affects the course of a given disease. However, in practice it is often wrongly regarded as a question about the summary treatment effect, which consists, as mentioned above, of three components. Doctors want to use drugs of proven effectiveness in this way, but in practice the assessment relates to the summary treatment effect. Unfortunately, this approach can also be attributed to the effective operation of drugs and methods that have no real impact on a given disease. Negative review of many popular drugs, used for years and recognized as effective, by comparison with placebo demonstrates how easy a process of treatment may be committing a mistake by assigning methods with no real impact on a disease [12]. The results of this study indicate that such a mistake can often occur in daily practice. The treating doctor is not able to even approximate the proportion of components of a summary treatment result in an individual patient. Seldom does he realize what great opportunities lie in the placebo effect.

The SPRT index easy to find on the basis of publicly available data adopted in the current work fairly well illustrates the relative proportions between the drug and placebo effects in the total power of the treatment. It allows one not only to communicatively define these proportions but also to be able to make an interesting comparison, allowing for closer insight into the essence of the placebo effect.

Undoubtedly, a disease and a method of its treatment affect perception of its environment, including the treatment effects and variation in size of the placebo effect. Characteristics of psyche, often on the border of pathology reported in numerous studies of patients suffering from allergic diseases and asthma, strongly predispose this group to succumb to a placebo effect. The present work clearly supports this view, stressing that a particular susceptibility to a placebo effect occurs in patients with rhinitis and when treatment results are valuated with clinical (subjective) measures. It is worth emphasizing the large differences in the placebo effect in these studies for the same drug used in the same disease, as also pointed out by other authors [11]. This justifies caution when interpreting the results of even the most methodologically correct and formal clinical trials of drugs used in treatment of allergic diseases and asthma.

Conclusions

1. The proportion of the placebo effect in high-quality studies of the effectiveness of individual anti-allergic and anti-asthmatic drugs is diverse and significantly higher than in similar studies with a drug used to treat hypertension – captopril.
2. The highest proportion of the placebo effect was found in studies of the effectiveness of treatment of allergic rhinitis and it was significantly higher than in the case of asthma and allergic skin diseases, which did not differ significantly.
3. A higher share of the placebo effect was observed in studies in which effectiveness of the drug was evaluated with subjective (clinical) indicators than objective.

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