

Placebo Effects in Clinical Trials Evaluating Patients with Uncontrolled Persistent Asthma

Faye Luc¹, Emily Prieur¹, G. A. Whitmore², Peter G. Gibson³, Katherine L. Vandemheen¹, and Shawn D. Aaron¹

¹The Ottawa Hospital Research Institute, University of Ottawa, Ottawa, Ontario, Canada; ²Desautels Faculty of Management, McGill University, Montreal, Quebec, Canada; and ³Department of Respiratory and Sleep Medicine, John Hunter Hospital, New Lambton Heights, New South Wales, Australia

ORCID ID: 0000-0002-4762-3542 (S.D.A.).

Abstract

Rationale: Patients with uncontrolled, persistent asthma can show substantial health improvements when administered placebo.

Objectives: We analyzed five randomized, placebo-controlled clinical trials that assessed subjects with uncontrolled, persistent asthma to determine the magnitudes of placebo effects across different clinical outcomes.

Methods: Placebo effects for objective asthma-related outcomes, healthcare utilization outcomes, and patient-reported outcomes were estimated, with adjustments for regression to the mean.

Results: Statistically significant improvements in all clinical outcomes were seen in patients randomized to placebo across all trials. Placebo effects were largest for healthcare utilization outcomes, including exacerbations (median reduction, 0.44 events/yr; 31% risk reduction; range, 19–56%), emergency department visits (median reduction, 0.19 events/yr; 50% risk reduction; range, 36–82%), and hospitalizations for asthma (median reduction, 0.26 events/yr; 66% risk reduction; range, 61–74%). Patient-reported outcomes exhibited intermediate placebo effects. Median

improvements in the Asthma Control Questionnaire and St. George's Respiratory Questionnaire scores in placebo-treated patients were 0.53 units (25% improvement; range, 18–30%) and 8.3 units (19.5% improvement; range 19–20%), respectively. Forced expiratory volume in 1 second exhibited the smallest relative placebo effects (median increase, 77 ml; 4.2% improvement; range, 3.4–4.9%). Subgroup analyses did not reveal patient subgroups that were more susceptible to placebo effects. Pre- and postrandomization counts for asthma exacerbations showed patterns consistent with the expected negative binomial distribution except for significant departures in prerandomization exacerbations for two trials.

Conclusions: Patients with uncontrolled asthma derived consistent benefit from randomization to placebo. Observed placebo effects may represent beneficial effects of both sham therapy and a structured asthma regimen dictated by the study protocol. In the case of healthcare utilization outcomes, recall errors in self-reported healthcare events may have introduced biases that inflated placebo effect estimates.

Keywords: asthma; asthma exacerbations; clinical trials; placebo effects

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Correspondence and requests for reprints should be addressed to Shawn D. Aaron, M.D., The Ottawa Hospital, General Campus, 501 Smyth Road, Ottawa, ON, K1H 8L6 Canada. E-mail: saaron@ohri.ca.

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A placebo is an inactive substance or sham form of therapy used as a control in clinical trials. Though lacking pharmacologic activity, placebos have been shown to improve signs and symptoms for a wide variety of human diseases both in research trials and in actual clinical practice (1). The phenomenon of improvement in patient health on taking an inactive treatment is

termed “the placebo effect” (2). In the case of randomized, placebo-controlled clinical trials examining treatment of chronic diseases, a study intervention or a placebo is administered in conjunction with a protocol that calls for a structured standard of clinical care delivered to both trial arms. Potential placebo effects seen under these conditions can thus be derived from a combination of 1)

administration of a sham medication, and 2) provision of a structured clinical regimen dictated by the study protocol (3).

Asthma is a respiratory disease characterized by chronic airway inflammation that results in variable expiratory airflow limitation as well as respiratory symptoms, including wheeze, dyspnea, chest tightness, and cough (4).

Although the symptoms associated with asthma are subjective by nature, one of the hallmarks of asthma is that changes in baseline lung function and changes in airway inflammation can occur rapidly with medical intervention, and these changes can be objectively quantified. As such, asthma can be an excellent disease model to study placebo effects (5).

A previous study by Wechsler and colleagues sought to assess the placebo effect in patients with stable asthma (6). The study included a drug intervention arm, a placebo intervention arm, and a no-intervention arm. The study found that placebo had no effect on forced expiratory volume in 1 second (FEV₁). Subjective improvements in asthma control were seen in the placebo intervention arm compared with the no-intervention arm (6). The magnitude of subjective improvements with placebo was comparable to that of the group treated with albuterol. These findings of improvements in asthma control in patients with mild, stable asthma treated with placebo have not been described in patients with more severe persistent uncontrolled asthma. Moreover, other important clinical outcomes related to healthcare utilization that may respond to placebo, such as exacerbation rates and hospitalizations, have not been studied. Whether all subjects with asthma or a select subgroup are susceptible to placebo effects is also largely unknown (7).

We analyzed the results of five placebo-controlled clinical trials that assessed treatments for subjects with uncontrolled, persistent asthma. Our objective was to determine whether the magnitudes of placebo effects vary between different clinical outcomes or vary depending on

characteristics of the study population and to determine how statistical methods can be used to isolate explanatory factors for these effects.

Methods

Data Sources

The five placebo-controlled clinical trials analyzed were the AMAZES (effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma) (8), MENSA (mepolizumab as adjunctive therapy in patients with severe asthma) (9), MUSCA (effect of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma) (10), and LAVOLTA (efficacy and safety of lebrikizumab in patients with uncontrolled asthma) I and LAVOLTA II trials (11). Table 1 describes the trial interventions, patient baseline characteristics for the placebo arm, and trial durations. The trials all enrolled patients with persistent, uncontrolled asthma. The MENSA and MUSCA trials stipulated that enrolled patients must have experienced at least two exacerbations requiring treatment with systemic corticosteroids in the previous 12 months. The other three trials did not prespecify a minimum exacerbation history. The five trials recorded prestudy exacerbations on the basis of the patient's history of events within the previous year. The AMAZES, MENSA, and MUSCA trials also recorded prestudy emergency visits and hospitalizations; however, these data were not available from the LAVOLTA I and II trials. None of the studies required objective verification of these events.

Statistical Analysis

The placebo effect for each outcome for each subject on the placebo arm was calculated as the arithmetic difference between the subject's outcome while on the placebo arm of the clinical trial and the anticipated outcome that would have been experienced if the subject had continued to live under prestudy conditions without trial participation. In cases where the study protocol restricted the study population on the basis of the outcome measure, the anticipated outcome was estimated by adjusting the prestudy outcome for regression to the mean (RM) (12). RM is a common phenomenon that is encountered when outcomes for subjects are observed in successive time periods. The phenomenon is seen when subjects who have an outlying outcome in a prestudy period are found to have outcomes closer to average in a follow-up on-study period (13). The MENSA and MUSCA studies both restricted enrollments to subjects with two or more total exacerbations in the prestudy year, and thus prestudy exacerbation counts for these studies were RM adjusted. A technical description of the RM adjustment is available in the online supplement.

The percent placebo effect for a subject was calculated as the percentage ratio of the subject's placebo effect to the subject's adjusted prerandomization outcome. Outcomes measures, including FEV₁, Asthma Control Questionnaire (ACQ), Asthma Quality of Life Questionnaire (AQLQ), and St. George's Respiratory Questionnaire (SGRQ) scores, were modeled as continuous variables. Confidence intervals for their placebo effects and percentage

Table 1. Characteristics of the placebo group for five randomized clinical trials used in the analysis of placebo effects

	AMAZES	MENSA	MUSCA	LAVOLTA I	LAVOLTA II
Intervention	Azithromycin vs. placebo	Mepolizumab vs. placebo	Mepolizumab vs. placebo	Lebrikizumab vs. placebo	Lebrikizumab vs. placebo
Duration, wk	48	32	24	52	52 wk
No. of subjects randomized to placebo group	207	191	277	362	354
Mean age (SD)	57 (15)	49 (12)	52 (14)	51 (12)	50 (13)
Female sex, n (%)	121 (58)	107 (56)	176 (64)	231 (64)	219 (62)
Mean baseline pre-BD FEV ₁ % predicted (SD)	73.6 (18.8)	62.4 (18.1)	55.2 (14.6)	61.0 (10.6)	61.1 (10.6)
Mean baseline ACQ score (SD)	1.55 (0.79)	2.28 (1.19)	2.2 (1.2)	2.69 (0.76)	2.77 (0.73)

Definition of abbreviations: ACQ = Asthma Control Questionnaire; AMAZES = effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma; BD = bronchodilator; FEV₁ = forced expiratory volume in 1 second; LAVOLTA = efficacy and safety of lebrikizumab in patients with uncontrolled asthma; MENSA = mepolizumab as adjunctive therapy in patients with severe asthma; MUSCA = effect of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma; SD = standard deviation.

placebo effects were calculated using formulas for simple random samples from normal distributions. Exacerbation counts, emergency visits, and hospital admissions in the prestudy and on-study periods were modeled as bivariate negative binomial distributions and are reported as annualized rates. The models were estimated by the maximum likelihood method.

Subgroup effects were explored using data from the AMAZES trial. Subgroup analyses involving prestudy fixed covariates (sex, age, ever smoked, symptom years, body mass index [BMI]) were treated as subpopulations. For time-varying covariates (FEV₁% predicted, blood eosinophil count), a single statistical model was fitted to the outcome measure, and RM-adjusted outcomes were assigned to their respective subgroup categories. Subgroup differences in placebo effects were tested using a Kruskal-Wallis one-way rank-based analysis of variance test.

Goodness-of-fit chi-square tests were performed to check the appropriateness of the negative binomial models for exacerbations, emergency visits, and hospital admissions. Statistical analysis was done using STATA 12 statistical software (StataCorp, College Station, TX). The study was approved by The Ottawa Health Science Network Research Ethics Board.

Results

Table 1 depicts characteristics of the patients randomized to the placebo arms in the five randomized clinical trials used in the analysis. Table 2 shows calculated placebo effects for asthma exacerbations, emergency department visits for asthma (without hospital admission), and hospital admissions for asthma. These three outcomes all relied on historical data collection to determine prestudy events. The median reduction in annual asthma

exacerbations in patients treated with placebo was 31% (range, 19–56% across the five studies). Median reductions in emergency department visits and hospital admissions experienced by patients treated with placebo were 50% (range, 36–82%) and 66% (range, 61–74%), respectively, across three studies.

Subjective patient-reported study outcomes measured directly on the day of randomization and at study end, such as ACQ, AQLQ, and SGRQ scores, are presented in Table 3. The median improvement in the ACQ score from time of randomization to the end of study in placebo-treated patients was 25% (range, 18–30% across the five studies). Observed placebo effects exceeded the minimal clinically important difference (MCID) of a 0.5 improvement in the ACQ score in 44% to 53% of subjects randomized to placebo. The SGRQ score was measured in the MENSA and MUSCA trials and improved by 19% and 20% in patients treated with placebo. In both these trials, 61% of subjects

Table 2. Calculated placebo effects for asthma exacerbations, emergency department visits, and hospital admissions for asthma

Outcome	AMAZES	MENSA	MUSCA	LAVOLTA I	LAVOLTA II
No. of subjects	207	191	277	362	354
Total exacerbations, events/yr					
Baseline mean	2.08	3.57	3.15	1.28	1.35
RM-adjusted baseline mean	—	2.69	2.15	—	—
End-of-treatment mean	1.68	1.86	1.82	0.84	0.61
Placebo effect (95% CI)	0.40 (0.04 to 0.76)	0.84 (0.46 to 1.21)	0.33 (0.17 to 0.50)	0.44 (0.11 to 0.77)	0.75 (0.44 to 1.05)
Percent placebo effect (95% CI)	19 (7 to 30)	31 (19 to 42)	19 (7 to 31)	34 (11 to 57)	56 (40 to 71)
Median percent placebo effect (range)	—	—	31 (19 to 56)	—	—
Emergency department visits without hospital admission, events/yr					
Baseline mean	0.29	0.38	0.23	*	*
End-of-treatment mean	0.05	0.19	0.15	—	—
Placebo effect (95% CI)	0.24 (0.19 to 0.30)	0.19 (0.09 to 0.29)	0.08 (−0.01 to 0.18)	—	—
Percent placebo effect (95% CI)	82 (65 to 91)	50 (20 to 69)	36 m (−7 to 61)	—	—
Median percent placebo effect (range)	—	—	50 (36 to 82)	—	—
Hospital admissions, events/yr					
Baseline mean	0.19	0.44	0.36	*	*
End-of-treatment mean	0.07	0.15	0.09	—	—
Placebo effect (95% CI)	0.12 (0.08 to 0.15)	0.29 (0.17 to 0.42)	0.26 (0.18 to 0.34)	—	—
Percent placebo effect (95% CI)	61 (28 to 79)	66 m (43 to 79)	74 (52 to 86)	—	—
Median percent placebo effect (range)	—	—	66 (61 to 74)	—	—

Definition of abbreviations: AMAZES = effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma; CI = confidence interval; LAVOLTA = efficacy and safety of lebrikizumab in patients with uncontrolled asthma; MENSA = mepolizumab as adjunctive therapy in patients with severe asthma; MUSCA = effect of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma; RM = regression to the mean.

*Data on emergency department visits and hospitalizations were not available from reported statistics for the LAVOLTA studies.

Table 3. Calculated placebo effects for subjective patient-reported study outcomes (ACQ, AQLQ, and SGRQ scores)

Outcome	AMAZES	MENSA	MUSCA	LAVOLTA I	LAVOLTA II
ACQ score					
Baseline mean	1.55	2.27	2.16	2.69	2.77
End-of-treatment mean	1.30	1.75	1.75	1.89	2.00
Placebo effect (95% CI)	0.25 (0.14–0.36)	0.53 (0.40–0.65)	0.40 (0.26–0.53)	0.80 (0.69–0.91)	0.77 (0.66–0.88)
Percent placebo effect (95% CI)	18 (10–25)	25 (19–31)	20 (13–27)	30 (26–34)	28 (24–32)
Median percentage placebo effect (range)			25 (18–30)		
Percentage of patients who experienced a placebo effect >MCID	44	53	49	*	*
AQLQ or SGRQ score					
Baseline mean	5.35 (AQLQ)	46.9 (SGRQ)	46.3 (SGRQ)	*	*
End-of-treatment mean	5.57	38.3	38.0		
Placebo effect (95% CI)	0.23 (0.10–0.35)	8.7 (6.6–10.9)	8.0 (6.1–10.0)		
Percentage placebo effect (95% CI)	4 (2–7)	20 (15–25)	19 (14–23)		
Percentage of patients who experienced a placebo effect >MCID	39	61	61		

Definition of abbreviations: ACQ = Asthma Control Questionnaire; AMAZES = effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma; AQLQ = Asthma Quality of Life Questionnaire; CI = confidence interval; LAVOLTA = efficacy and safety of lebrikizumab in patients with uncontrolled asthma; MENSA = mepolizumab as adjunctive therapy in patients with severe asthma; MUSCA = effect of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma; MCID = minimal clinically important difference: 0.5 units for ACQ and AQLQ and 4 units for SGRQ; SGRQ = St. George's Respiratory Questionnaire.

*Summary statistics for baseline AQLQ scores were not available from the published LAVOLTA studies; therefore percent placebo effects could not be calculated.

randomized to placebo exceeded the MCID of a 4-unit improvement in SGRQ score.

Objective study outcomes measured directly on the day of randomization and at study end, such as the FEV₁, exhibited the smallest relative placebo effects across the five studies. The median placebo increase in FEV₁ was 4.2% (range, 3.4–4.9% across the five trials) (Table 4). Summary placebo effects for six evaluated outcomes across the five individual trials are depicted in Figure 1.

Analysis of potentially relevant patient subgroups from the AMAZES trial, including sex, age, smoking status, years of symptoms, BMI, baseline FEV₁% predicted, and baseline blood eosinophil count is shown in Table E1 in the online supplement. The analysis did not reveal any patient subgroup variables in which placebo effects differed significantly across subgroup categories.

Table E2 summarizes results from goodness-of-fit tests of the negative binomial model for the AMAZES, MENSA,

and MUSCA studies. Exacerbations experienced during the actual study period fit the model for all three studies. Exacerbations experienced in the prestudy period for the AMAZES study also showed a good fit (chi-square test, $P=0.37$). Exacerbations experienced in the prestudy period for both the MENSA and MUSCA studies exhibited a significant departure from the negative binomial distribution (test chi-square, $P<0.001$ in both cases). Most striking is an unusually large number of

Table 4. Calculated placebo effect for change in forced expiratory volume in 1 second

FEV ₁ volume (L)	AMAZES	MENSA	MUSCA	LAVOLTA I	LAVOLTA II
Baseline mean	2.12	1.86	1.81	1.85	1.89
End-of-treatment mean	2.18	1.94	1.87	1.93	1.98
Placebo effect (95% CI)	0.065 (0.034–0.097)	0.084 (0.028–0.140)	0.061 (0.014–0.107)	0.077 (0.037–0.116)	0.093 (0.051–0.135)
Percent placebo effect (95% CI)	3.4 (1.8–5.1)	4.8 (1.7–7.9)	4.0 (1.3–6.7)	4.2 (2.0–6.3)	4.9 (2.7–7.2)
Median percent placebo effect (range)			4.2 (3.4–4.9)		

Definition of abbreviations: AMAZES = effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma; CI = confidence interval; FEV₁ = forced expiratory volume in 1 second; LAVOLTA = efficacy and safety of lebrikizumab in patients with uncontrolled asthma; MENSA = mepolizumab as adjunctive therapy in patients with severe asthma; MUSCA = effect of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma.

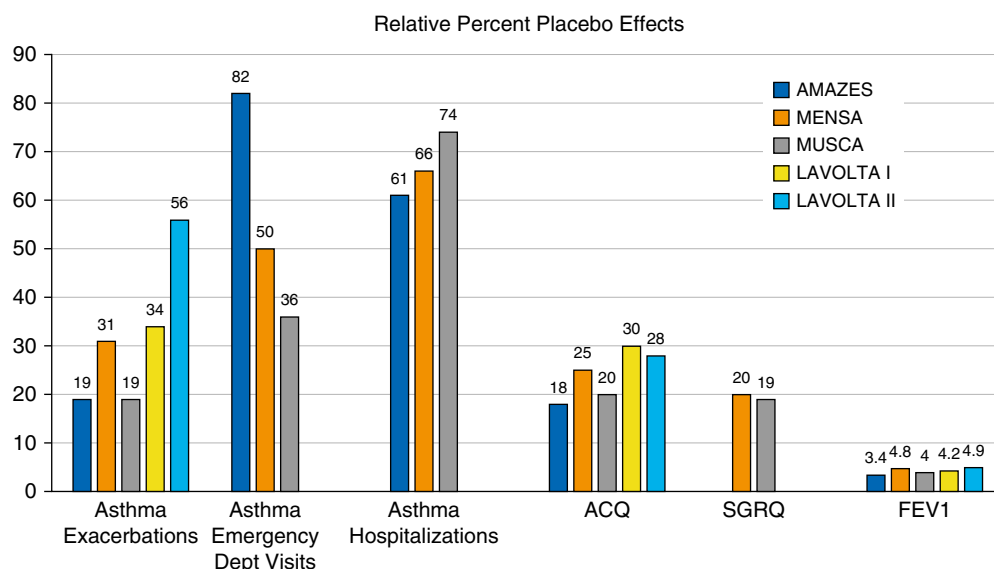


Figure 1. Summary placebo effects for evaluated outcomes across the five individual trials. ACQ = Asthma Control Questionnaire; AMAZES = effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma; FEV₁ = forced expiratory volume in 1 second; LAVOLTA = efficacy and safety of lebrikizumab in patients with uncontrolled asthma; MENSA = mepolizumab as adjunctive therapy in patients with severe asthma; MUSCA = effect of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma; SGRQ = St. George's Respiratory Questionnaire.

subjects in the MUSCA study who reported experiencing exactly two exacerbations during the prestudy year (Figure 2).

Discussion

Our analysis of patients with uncontrolled, persistent asthma revealed consistent statistically significant improvements in all clinical outcomes for patients treated with

placebo across all five randomized trials. Placebo effects were largest for outcomes that relied on historical data collection to determine prestudy events, such as annual hospitalizations, emergency department visits, and exacerbations for asthma, and were lowest for objective study outcomes measured directly on the day of randomization, such as FEV₁. For patient-reported outcomes, the magnitude of the placebo effect exceeded the MCID in 39% to

61% of cases (median, 51%), depending on the specific study and outcome. Our study analysis did not reveal any patient subgroups that were differentially susceptible to placebo effects.

What factors might explain significant beneficial placebo effects in patients with severe, uncontrolled asthma? Contributing factors to placebo effects could include: 1) neurobiological mechanisms mediating placebo effects, 2) psychological factors arising from expectations of benefit, 3) better-than-usual clinical monitoring and patient care by the study team during the trial period, 4) better subject adherence to baseline asthma medications and therapies while on the study, and 5) beneficial self-prompted changes in life style by subjects not explicitly prescribed in the study protocol. In addition, statistical artifacts, such as RM and recall bias (where applicable), must also be considered as potential causes of apparent placebo effects.

Research suggest that placebo effects potentially work through neurobiological mechanisms. Brain imaging has shown intracortical circuitry that produces placebo-related analgesia, suggesting that neurobiological processes may help mediate the placebo effect (14, 15). In one study involving patients suffering from chronic pain, placebo responders showed higher

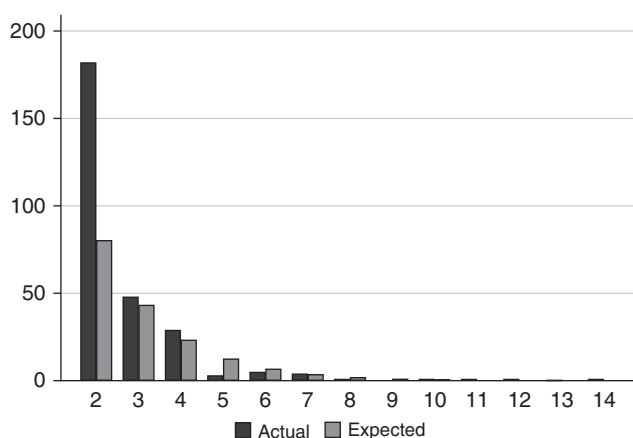


Figure 2. Prestudy frequency distribution of exacerbation counts for the MUSCA (effect of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma) study. Black bars represent the actual prestudy frequency distribution of exacerbation counts in the MUSCA study, in which subjects were required to have two or more exacerbations. The gray bars represent the expected frequency distribution based on fitting a negative binomial distribution. An excess of subjects having exactly two exacerbations is apparent.

concentration of endorphins in the brain than placebo nonresponders (16).

Psychological processes, such as classical conditioning and expectancy, also play a role (17). Studies have revealed that conditioning participants produces expectancies, which can then elicit significant placebo responses (18, 19). Most patients who enter clinical trials are subject to some degree of conditioning, with anticipation that entry into the study will improve some aspects of their underlying disease (20). These preconditioned subjects may develop expectations of improvement that can mediate placebo responses (19, 20). Recent research in cognitive science suggests that the brain may operate automatically to mediate a placebo response without conscious patient awareness (21).

Other explanations, such as increased adherence to maintenance medications, may underlie the observed placebo effect in asthma clinical trials. Subjects who enroll in clinical trials will often have their usual asthma medications provided free of charge by the study sponsor after study randomization. Those subjects who were previously unable to afford some, or all, of their prescribed asthma therapies may exhibit improvements in asthma control after a study begins once their usual asthma medications are provided without cost. In addition, because of increased medical attention and scrutiny, patients with asthma who participate in clinical trials may adhere more rigorously to their prescribed asthma therapies, and this increased adherence to therapy may result in improved asthma control even in patients who receive placebo (7). An increased frequency of visits to healthcare professionals as mandated by study protocols, and increased intensity of medical care provided by study physicians, may also result in improved clinical care for study patients leading to consequent placebo responses and improvements in asthma control (20). Finally, on trial enrollment, patients may be inclined to pay more attention to diet, exercise, and avoidance of exposures to allergens and other asthma triggers, all behaviors that may improve asthma control (22).

A study done by Hróbjartsson and colleagues investigated more than 100 clinical trials focusing exclusively on the health benefits of placebo treatment compared with no treatment at all (23). Their findings concluded that subjective outcome measures are more likely to be

impacted by the placebo effect, whereas objective outcome measures are less likely to be influenced by it. Wechsler and colleagues observed similar results when studying placebo effects in patients with stable asthma (6). How then to reconcile the results of our study, which suggest that three apparent objective outcomes (asthma exacerbations, emergency department visits, and hospital admission) were most influenced by placebo? One possibility is that better attention to medication adherence and more frequent and intense medical follow-up associated with being in the clinical trial prevented some of these clinical events. In addition, more intense clinical care and follow-up may have allowed for earlier detection and treatment of any exacerbation events experienced during the study period, thus preventing subsequent emergency department visits and hospitalizations. Our study results lend some support to the latter theory, because results of our analysis suggest that the magnitude of the placebo effect was greater for emergency department visits and hospitalizations than it was for exacerbations.

However, an analysis of our data also suggests that the placebo effects for these outcomes may have been potentially distorted by recall biases producing faulty estimates of prestudy exacerbations, emergency visits, and hospital admissions. The trials used in our analysis recorded prestudy exacerbations, emergency visits, and hospitalizations on the basis of the patient's recall of events within the previous year; however, it appears that none of the five studies required objective verification of these events through a review of the patients' written medical records. Therefore, these outcomes might be affected by recall bias, because they depend solely on the patients' memory of events (24). Our analysis showed no departure from the negative binomial model for exacerbations experienced in the prestudy period for the AMAZES study but statistically significant departures for both the MENSA and MUSCA studies. In contrast, exacerbations experienced during the actual study period fit the expected negative binomial distribution for these studies. These findings suggest that biases may be producing artificially inflated estimates of prestudy exacerbation and admission rates (24).

Estimated placebo effects for healthcare utilization outcomes may be distorted by

self-response errors, creating potential bias. However, we believe that the estimates are valuable irrespective of potential bias. If there is no average response bias for baseline health utilization counts, then the large placebo effects are clinically important and meaningful. If baseline health utilization counts are subject to large response biases, then this has important implications, because historical exacerbation and hospitalization outcomes are frequently used in practice to phenotype patients and to choose which patients would qualify for add-on monoclonal antibody therapies.

Previous studies have shown that patient recall of respiratory exacerbations is poor. In the Subpopulations and Intermediate Outcome Measures in Chronic Obstructive Pulmonary Disease (COPD) study, 68 subjects with COPD had questionnaires taken at baseline and then again 6 weeks later to determine whether they had experienced COPD exacerbations in the previous year. There was a disparity in patient responses at baseline and 6 weeks later in 20 of 68 subjects (29%). Six patients reported more exacerbations experienced within the previous year at 6 weeks than at baseline, and 14 reported fewer exacerbations (25). This suggests that patient recall of exacerbation events can be faulty. Some of this error may be due to patients "telescoping" the recall interval, whereby the previous year, say, is mistakenly lengthened or shortened when mentally recalling events, thereby producing a faulty count.

One final consideration is that an unusually large number of subjects in the MUSCA study reported experiencing exactly two exacerbations during the prestudy year (Figure 2), and this was also a criterion for entry into the study. It is thus possible that patients, or their study physicians, may have artificially inflated their prestudy exacerbation counts to gain entrance into the clinical trial. Unfortunately, we do not have access to patients' prestudy medical records to verify this hypothesis.

The main strength of our study is the in-depth statistical analyses of placebo effects in clinical trials related to persistent, uncontrolled asthma across multiple studies. Investigating numerous outcome measures allowed estimation of the magnitudes of placebo effects for important objective and subjective outcome measures associated with asthma. Our analysis also included multiple subgroup analyses from

the AMAZES study to determine if there were significant differences in placebo effects between key subpopulations of patients with asthma.

A limitation of our study is that only five separate clinical trials are included in the analyses. A larger number of studies could provide more precise estimates for placebo effects. Our subgroup analyses focused on patients' demographics and biomarkers, but we did not have access to psychological assessments of these patients. Examination

of the personality traits of patients might provide further insight into which patients are more prone to being "placebo responders."

To conclude, the findings of this study have confirmed the presence of significant placebo effects in clinical trials of patients with persistent, uncontrolled asthma, as well as clear differences in placebo effect sizes for various outcome measures. Placebo effects were largest for clinically important outcomes related to healthcare

utilization. The observed placebo effects may be derived from direct beneficial effects of sham therapy as well as benefits derived from a structured clinical asthma regimen dictated by the study protocol. In the case of healthcare utilization outcomes, our data also suggest that recall biases may be partially responsible for producing artificially inflated placebo effect estimates. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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ONLINE DATA SUPPLEMENT

"PLACEBO EFFECTS" IN CLINICAL TRIALS EVALUATING PATIENTS WITH UNCONTROLLED PERSISTENT ASTHMA

Faye Luc, Emily Prieur, GA Whitmore, Peter G Gibson, Katherine L Vandemheen,
Shawn D. Aaron

S.1 Subgroup Analyses for the AMAZES Study

Table S-1: Analysis of placebo effects in patient subgroups

Subgroup		Total Exacerbations		ED Visits		Hospital Admissions		ACQ Score		AQLQ Score		FEV1	
		Percent Placebo Effect	P-value	Percent Placebo Effect	P-value	Percent Placebo Effect	P-value	Percent Placebo Effect	P-value	Percent Placebo Effect	P-value	Percent Placebo Effect	P-value
Sex	Women (N=121)	23.7	0.602	86.1	0.821	59.9	0.585	21.5	0.106	5.3	0.136	4.8	0.248
	Men (N=86)	11.7		75.4		63.9		12.3		2.7		1.6	
Age	≤ 60 (N=106)	42.2	0.050	85.6	0.375	68.5	0.684	17.5	0.926	4.5	0.258	4.5	0.056
	> 60 (N=101)	-44.4		72.9		32.3		17.8		3.9		1.5	
Ever Smoked	No (N=126)	17.8	0.277	87.3	0.303	56.7	0.321	14.3	0.294	3.3	0.219	3.0	0.908
	Yes (N=81)	21.9		75.9		69.0		22.0		5.7		4.2	
Years of Symptoms	≤ 15 (N=112)	26.0	0.848	80.9	0.453	54.9	0.358	15.2	0.261	3.8	0.670	4.2	0.406
	> 15 (N=95)	8.5		84.0		71.1		21.4		4.7		2.5	
BMI	< 25 (N=42)	20.2	0.086	86.5	0.558	45.8	0.797	10.1	0.195	4.4	0.908	2.2	0.763
	≥ 25 (N=164)	19.6		83.6		62.9		18.4		4.2		3.8	
FEV1 % Predicted (%pts)	< 50 (N=22)	21.0	0.183	85.8	0.640	54.4	0.807	17.1	0.728	-0.7	0.687	1.5	0.592
	≥ 50 to < 80 (N=108)	20.1		79.1		59.3		20.9		4.2		3.7	
	≥ 80 (N=76)	17.1		85.4		66.6		13.3		5.8		3.7	
Blood Eosinophil Count (x 10 ⁹)	< 0.3 (N=108)	31.2	0.429	87.9	0.877	64.4	0.845	22.7	0.165	5.1	0.357	2.3	0.495
	≥ 0.3 (N=98)	5.6		78.5		57.2		11.1		3.3		4.7	

S.2 Goodness of Fit Test Results

Table S-2: P-values for chi-square tests of fit for marginal frequency distributions of total exacerbations, ED visits without hospital admissions, and hospital admissions for three studies to assess consistency with a negative binomial distribution.

Outcome³	AMAZES	MENSA	MUSCA
Pre-randomization exacerbations	0.369	<0.001 ²	<0.001 ²
On-study exacerbations	0.440	0.236	0.031
Pre-randomization ED visits w/o hosp. adm.	0.653	0.220	0.155
On-study ED visits w/o hosp. adm.	n.a. ¹	n.a. ¹	n.a. ¹
Pre-randomization hosp. adm.	n.a. ¹	0.641	0.031
On-study hosp. adm.	n.a. ¹	n.a. ¹	n.a. ¹

Footnotes:

1. Not available (n.a.): Too few frequency classes available to conduct a chi-square test.
2. Chi-square test applied to the frequency distribution of 2 or more exacerbations.
3. Largest exacerbation counts are pooled in a single class having frequency 5 or more.

S.3 Theory and Methods for Regression-to-the-Mean Adjustments

Introduction

This supplement describes the mathematical basis of adjustments for regression-to-the-mean (abbreviated RM). We first present our definition of a placebo effect and explain why and how adjustments for RM arise in connection with estimating these effects. We then consider two contexts requiring RM adjustments that are encountered in our study: (1) bivariate continuous outcome variables and (2) bivariate discrete outcome variables.

Outcome variables for asthma studies are variables that are time-varying for individual subjects. Our outcomes include three count variables, number of acute exacerbations, number of emergency department visits and number of hospital admissions, and four continuous outcome variables, FEV1 lung volume, ACQ score, AQLQ score, and SGRQ score. The placebo and treatment effects for these outcomes were adjusted for RM as required.

Definition of a Placebo Effect

A placebo effect in a clinical trial is an apparent benefit to a subject that is created by simply participating in the trial but unknowingly receiving no therapeutic intervention. The placebo effect for a given outcome variable is the measured difference between the outcome realized from being assigned to the placebo arm of the trial and the outcome that would be experienced if the subject had continued to live in the pre-study environment without trial participation. The phrase "would be experienced" reminds us that a *counter-factual* is involved in measuring a placebo effect. We must anticipate what cannot be observed directly, namely, the subject's outcome if he or she had not been enrolled in the clinical trial. Clearly, the outcome experienced by the subject in the pre-study period of the clinical trial gives us a clue to the value of this counter-factual. We exploit this connection in the technical development that follows.

Let Y_0 and Y_1 be generic notation for the outcome values for a subject in the pre-study period (period 0) and the on-study period (period 1), respectively. The counter-factual outcome is the one that would occur in the on-study period *if the pre-study causal environment were to continue into the on-study period*. We denote this counter-factual outcome value by Y_* . This quantity represents the outcome value that would be observed without the study intervention and is an unobservable quantity. We need to anticipate the value of Y_* so it can be compared to the actual outcome Y_1 in the on-study period. We denote this anticipated value by Y_{RM} . We will use an estimate of the mean of Y_* as the anticipated value Y_{RM} . The *arithmetic difference* $Y_1 - Y_{RM}$ is the estimated *individual placebo effect* for the subject for the outcome variable. The percentage difference $100(Y_1 - Y_{RM})/Y_{RM}$ is the estimated *individual percent placebo effect* for the subject. The percentage change is undefined if $Y_{RM} = 0$. By convention, we define the sign of the placebo effect so it is positive for more a beneficial outcome (for example, fewer exacerbations are better while larger FEV1 volumes are better). To follow this convention, we will reverse the difference $Y_1 - Y_{RM}$ as needed.

Adjustment Methods for Regression to the Mean

We first describe regression to the mean in generic terms. Consider a subject from the study population and let (Y_0, Y_*) denote two independent and identically distributed outcomes in successive time periods of the same length. As already defined, Y_0 is the subject's observed outcome during the pre-study period and Y_* is the outcome that would be experienced by the same subject

in the follow-up period if causal conditions remain unchanged (the counter-factual outcome). If μ_0 is the mean pre-study outcome for all subjects in the study population, that is, $E(Y_0) = \mu_0$ then the anticipated mean value of Y_* , conditional on Y_0 , is given by:

$$E(Y_*|Y_0) = (1 - \omega)\mu_0 + \omega Y_0. \quad (1)$$

Notation $E(\cdot)$ and $E(\cdot|\cdot)$ represent marginal and conditional expected values of random variables. Symbol ω is a fractional parameter ($0 < \omega < 1$) that remains to be defined. Observe that the expected outcome of Y_* is a weighted average of the observed outcome Y_0 for the individual subject and the study population mean μ_0 . Because the weight ω is a fraction, the weighting causes ‘shrinkage’ of Y_0 toward the population mean μ_0 . In other words, the outcome in the follow-up period will tend to be closer to the population mean, on average, than the observed outcome in the pre-study period (period 0). We now work through the several scenarios for RM encountered in our research program.

Continuous Outcome Variable

We start by considering a continuous outcome variable Y that is normally distributed. The pre-study outcome and its on-study counter-factual for an individual subject, that is, random pair (Y_0, Y_*) , are assumed to be independent and identically distributed normal random variables. We use $N(\mu, \sigma^2)$ to denote their distribution, where μ and σ^2 are their mean and variance, respectively. The mean parameter μ for a subject is itself randomly chosen from a normal distribution $N(\mu_M, \sigma_M^2)$. As a consequence of this model construction, the pair (Y_0, Y_*) for a subject who is randomly chosen from the study population has a correlated bivariate normal distribution. The marginal distributions are identical normal distributions $N(\mu, \sigma^2 + \sigma_M^2)$ and the correlation coefficient of the bivariate distribution is $\sigma_M^2/(\sigma^2 + \sigma_M^2)$. We see that although the successive outcomes Y_0 and Y_* are independent for an individual subject, the pairs of outcomes are positively correlated for the population of subjects because different subjects possess difference mean values. We now proceed to apply this model to estimating the placebo effect for a continuous outcome measure.

Consider a random sample of subjects from the placebo study population (or a subpopulation of interest). We denote this sample group by G . We estimate the anticipated outcome value Y_{RM} by first taking a simple linear regression of Y_1 on Y_0 for all subjects in G . We then rearrange terms of the regression function as follows:

$$\begin{aligned} \hat{Y}_1 &= b_0 + b_1 Y_0 = m_1 + b_1(Y_0 - m_0) \\ &= (m_1 - m_0) + [m_0(1 - b_1) + b_1 Y_0]. \end{aligned} \quad (2)$$

Here b_0 and b_1 are estimated regression coefficients. Notation $\hat{Y}_1$ is the fitted value of Y_1 , and m_0 and m_1 are the sample mean values of Y_0 and Y_1 for subjects in G . The quantity:

$$Y_{RM} = m_0(1 - b_1) + b_1 Y_0 \quad (3)$$

on the right-hand side of (2) is our desired estimate of counter-factual outcome Y_* . The equation for Y_{RM} has the conventional form of an RM estimate, being a weighted sum of the overall mean m_0 for all subjects in group G and the actual pre-study outcome Y_0 for the specific subject

in G . The arithmetic and percent placebo effects for the subject are given by $Y_1 - Y_{RM}$ and $100(Y_1 - Y_{RM})/Y_{RM}$, respectively.

As m_0 is the mean of the Y_0 values in group G , we see that the mean value of Y_{RM} for subjects in G equals m_0 . Thus, the estimated mean of individual placebo effects $Y_1 - Y_{RM}$ for subjects in group G is $m_1 - m_0$. This result shows that the RM adjustment at the individual level washes out when averaged over all subjects in the group. The estimated mean percent placebo effect is the mean of the individual percent placebo effects $100(Y_1 - Y_{RM})/Y_{RM}$. In general, this mean of individual percent relatives will not exactly match the percentage change in means $100(m_1 - m_0)/m_0$. Thus, the RM-adjustment in (3) must be made in order to compute an average percent placebo effect in group G .

Although we have motivated (3) using a bivariate normal distribution for the pair (Y_0, Y_*) , in applications where the normal distribution is only a rough approximation, we can still employ the same formula but estimate regression coefficient b_1 using the method of least-squares. A confidence interval for the mean placebo effect is computed from the sample mean $m_1 - m_0$ and the sample standard deviation of individual differences $Y_1 - Y_{RM}$ using the conventional large-sample formula for confidence limits.

Discrete Outcome Variable

We now consider discrete outcomes variables and, specifically, outcomes that are counting variables such as acute exacerbations, emergency department visits and hospital admissions. We refer to exacerbations in the description that follows.

As noted in the main text, there is a long history in the asthma literature of using the negative binomial distribution to describe the frequency distribution of exacerbations. The genesis of the negative binomial distribution is the following. It is taken as plausible that individual subjects experience a Poisson number of exacerbations in any observation period. The supporting argument is that exacerbations experienced by a subject are rare events that occur over time in a random pattern. Clinical experience tends to support the assumption. Under steady-state causal conditions, the Poisson distribution has a mean rate λ that is particular to the individual subject. Rate λ is assumed to vary across subjects according to a gamma distribution $\Gamma(\alpha, \beta)$. In this notation, the gamma distribution has mean $\mu = \alpha/\beta$. This gamma mixture of Poisson distributions for a population of subjects produces a negative binomial (NB) probability distribution for the population-level frequency distribution of exacerbations. The negative binomial distribution has excess variability compared to a Poisson distribution with the same mean μ .

The negative binomial model for the population distribution of asthma exacerbations exhibits regression to the mean when observed numbers of exacerbations are followed through successive time periods. To model pairs of exacerbation counts (Y_0, Y_1) in the pre-study and on-study periods, we require a special bivariate negative binomial (BNB) distribution. We assume that a given subject experiences independent Poisson counts of exacerbations in the two periods. For the moment, we assume that the two periods are of equal duration. Exacerbation rates in the two periods can differ for a subject. We denote these rates by λ_0 and $\lambda_1 = \zeta\lambda_0$, where subscript 0 denotes the pre-study period and subscript 1 denotes the on-study period for the placebo arm. Notice that these two exacerbation rates share the same baseline rate parameter λ_0 , which we assume as before has a gamma distribution $\Gamma(\alpha, \beta)$ in the study population. The parameter ζ is a multiplier that shrinks (or amplifies) the exacerbation rate between period 0 and period

1. Our model assumes therefore that the placebo effect has a proportionate impact ζ on the mean occurrence rate for exacerbations. No placebo effect is present if $\zeta = 1$. The distribution of (Y_0, Y_1) in the presence of placebo parameter ζ is the following bivariate negative binomial distribution:

$$P(y_0, y_1) = \zeta^{y_1} \frac{\beta^\alpha \Gamma(\alpha + y_0 + y_1)}{\Gamma(\alpha) y_0! y_1! (1 + \zeta + \beta)^{\alpha + y_0 + y_1}}. \quad (4)$$

It can be shown that the conditional distribution of $Y_1|Y_0$ is also a negative binomial distribution and, in particular, the conditional distribution has the following mean value:

$$E(Y_1|Y_0, \zeta) = \zeta E(Y_*|Y_0). \quad (5)$$

The right-hand quantity $E(Y_*|Y_0)$ is the RM-adjusted expectation given in (1) with $\mu_0 = \alpha/\beta$ and $\omega = 1/(1 + \beta)$. Formula (5) shows that the placebo effect shrinks the expected exacerbation count by a fixed proportion ζ .

The expected placebo effect for this model, conditional on Y_0 , equals $E(Y_* - Y_1|Y_0, \zeta) = (1 - \zeta)E(Y_*|Y_0)$. Notice here that we have reversed Y_* and Y_1 in defining the placebo effect because we anticipate that exacerbations will be lower on the placebo arm than under pre-study conditions. We take the corresponding theoretical percent placebo effect to be $100(1 - \zeta)$.

We estimate the bivariate negative binomial model (4) by the method of maximum likelihood using the pairs of sample exacerbation counts (Y_0, Y_1) for the subjects in group G . We plug maximum likelihood estimates of parameters α and β into expressions $\mu_0 = \alpha/\beta$ and $\omega = 1/(1 + \beta)$ and then use formula (1) to calculate the anticipated mean exacerbation rate Y_{RM} from which the individual placebo effect $Y_{RM} - Y_1$ or the percent placebo effect $100(Y_{RM} - Y_1)/Y_{RM}$ can be calculated. The BNB model, fitted by the maximum likelihood method, provides asymptotic confidence intervals for the theoretical placebo effect and percent placebo effect.

In situations where the pre-study and on-study periods have different time durations we require a simple adjustment. If the pre-study period is taken as a unit time length (say one year) then we let t be the length of the on-study period in the same units. For example, a 32-week on-study period would give $t = 32/52$ of a year. The analysis proceeds as before but now ζ is replaced by $t\zeta$ in (4). In essence, the exacerbation rates in the two periods are now related by $\lambda_1 = t\zeta\lambda_0$.

Subgroup Analysis

Consider subpopulations of the study population defined by a fixed subgroup variable, such as sex, ever smoked, and the like. If $G_k, 1 = 1, 2, \dots, K$, are K groups defined by this subgroup variable then the individual placebo effects for subjects within each of these subgroups can be estimated in the manner just described for a single group. Each subgroup is, in effect, a sample from a study subpopulation. A separate RM function is computed for each subgroup. For example, the subgroup variable sex defines two subpopulations and RM adjustments can be estimated for men and women using separate regression models. Our study does not consider cross-classifications of subgroup variables such as sex and age.

We distinguish subgroup variables that define fixed subpopulations from subgroup variables that classify subjects into categories whose boundaries or limits are correlated with the outcome variable Y_* or Y_1 . For example, consider subjects classified by FEV1 percent predicted categories

(under 50%, 50%-under 80%, 80% or more) for the outcome measure FEV1 volume (in liters). Variables FEV1 percent predicted and FEV1 volume are, of course, correlated variables across time for an individual subject. As another example, the subgrouping variable might be the outcome variable itself. For example, subjects can be classified by number of exacerbations in the pre-study period in a subgroup analysis of placebo effects for exacerbation counts. We handle this situation differently from subgroups whose composition is unchanging through time (such as sex groups). With time-varying subgroup variables, subjects can migrate in and out of their categories across time.

For a continuous outcome variable, we again denote the subgroups by $G_k, k = 1, 2, \dots, K$. We proceed by, first, estimating the regression function (2) for group G as a whole (pooling groups G_k) and, second, computing the individual placebo effect and percent placebo effect for each subject. We then average the individual placebo effects and percent placebo effects for subjects within each subgroup $G_k, k = 1, 2, \dots, K$. The average placebo effect in group G_k , for example, is given by $m_{1k} - m_{RMk}$ where m_{1k} and m_{RMk} are the sample mean values of Y_1 and Y_{RM} for subjects in subgroup G_k .

We have a research interest in knowing if placebo effects differ on average across subgroups for a continuous outcome variable. We test for significant differences in the mean placebo effects across subgroups $G_k, 1 = 1, 2, \dots, K$, by conducting a one-way ANOVA using the individual placebo effects $Y_1 - Y_{RM}$ as observations and the subgroups as the categorical variable. Because of potential departures from normality we employ a non-parametric rank-based one-way ANOVA known as the Kruskal-Wallis test. The test version that corrects for ties is used. The same ANOVA test is used as an approximate test for percent placebo effects also.

For discrete outcome variables, tests for differences in placebo effects and percent placebo effects across subgroups is handled as we have just described for continuous outcome measures except that the BNB distribution in (4) is used for estimation. Again, differences across subgroups is tested using the Kruskal-Wallis test with a correction for ties. This non-parametric test method is robust to the irregular residual distributions that are encountered with negative binomial data. Regression structures for parameters can also be incorporated into the BNB model to test for subgroup effects but the non-parametric ANOVA test is favored because it avoids over-reliance on BNB model assumptions.