Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Wechsler ME, Kelley JM, Boyd IOE, et al. Active albuterol or placebo, sham acupuncture, or no intervention in asthma. N Engl J Med 2011;365:119-26.

Active or placebo albuterol, sham acupuncture or no treatment in asthma

Online Repository

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Online Repository

I. Methods

1. Study Structure and visits:

Consent and Screening Visit: After obtaining written informed consent approved by the Brigham & Women's Hospital (BWH) Institutional Review Board, eligible subjects who had withheld acute bronchodilator therapy for a minimum of 8 hours, and long-acting bronchodilator therapy for at least 24 hours, completed medical history questionnaires including the Asthma Control Questionnaire[1] as well as the Personality Assessment Inventory (PAI) and the NEO Personality Inventory (see online repository table 2), and performed bronchodilator reversibility testing with 2 puffs of albuterol.[2] Subjects with a post-bronchodilator FEV_1 that was at least 12% higher than baseline were eligible to continue in the study and were invited to return to the BWH Asthma Research Center (ARC) for the first study visit within 3-7 days time.[3] For subsequent visits, short-acting inhalers were withheld for at least 8 hours and long-acting bronchodilators for at least 24 hours.

Treatment Visits 1-12: Upon return to the ARC within 3-7 days of the previous visit, subjects underwent baseline spirometry following assessment of exhaled nitric oxide utilizing a Niox Mino device . To maintain blinding of the spirometry technician, subjects were brought into a separate treatment room by a different research assistant who informed them that they would receive one of the following interventions on that day: an inhaled medicine (active or placebo), acupuncture (genuine or placebo), or observation of natural history. The inhaled placebos contained only propellant and inert

ingredients and were identical in appearance to albuterol inhalers. The validated sham acupuncture device looks and feels like an acupuncture needle, but instead of penetrating the skin, the needle telescopes into the shaft of the needle handle.[4] Subjects were not made aware of the fact that only sham acupuncture was ever performed in this study. To keep the spirometry technician blind, subjects were kept in the treatment room for ten minutes, even if they were assigned to the "no treatment" control condition. Aside from not receiving treatment, subjects assigned to the "no treatment" control condition were treated identically to those receiving treatment. It is important to note that the "no treatment" control condition differs from natural history as the " no treatment" condition controls for a myriad of non-specific factors, including attention from study staff, responses to repeated spirometry, regression to the mean, natural physiologic variation, and any effects arising from the hospital setting.

After baseline spirometry for each visit was performed, subjects underwent that visit's intervention (randomized within the 4 visits of that visit block), followed by repeated spirometry every 20 minutes for 2 hours. Subjects also completed questionnaires assessing subjective improvement in asthma symptoms, and, as an assessment of blinding, whether they knew which specific intervention they received (i.e., did they think they received genuine medication or genuine acupuncture?). Subjects then returned to the ARC for the subsequent eleven study visits within 3-7 days of each previous visit until placebo and genuine inhalers, sham acupuncture, and "no treatment" control were each administered 3 times (a total of 12 sessions). Subjects completing all study procedures were compensated up to $775. Subjects were also invited to return for a final visit in which open label albuterol was given to assess a final bronchodilator

response. This visit was intended to assess the difference in response to open label bronchodilator before and after the study, since there can be day to day or month to month variability to bronchodilator. Furthermore we wanted to assess whether or not there was a significant difference in response to open label vs. blinded bronchodilator therapy. The interventions were administered in a blocked randomized cross-over design as shown in **Figure 1**. This blocked design was selected to ensure that each intervention was administered once in each "epoch" of the study in order to control for subtle changes in asthma activity that could naturally occur over the course of the study. Within each block, the order of interventions was randomized to minimize any possible carry-over effects. Subject visits and spirometry were all done within the same 3 hour windows on visit days to minimize the effect of diurnal variation on study outcomes.

2. Blinding

Both the subjects and those who performed spirometry were blinded to treatment intervention. We assessed blinding immediately after treatment by asking subjects whether they thought the treatment they had received was genuine or placebo. We did not assess blinding when subjects were assigned to the "no treatment" control condition. Subjects were also blinded to all spirometry results**.**

Subjective Outcome: Subjective improvement was measured every 20 minutes post intervention using a visual analog scale. Since there were no pre-existing measures of subjective outcome for acute responses to asthma treatment, we created our own measure, modeled on visual analog scales that are commonly used in medicine to measure subjective patient-centered complaints.[5,6,7] Our measure included numerical anchors

ranging from 0 to 10, as well as explicit designations for the endpoints ("0 = no improvement at all" and "10 = complete improvement"). The text of the question was "Please circle on the 10-point scale below your rating of how much your breathing has improved today. We then converted this to percent improvement by multiplying each score by 10. This measure was taken at the same 20 minute intervals as for spirometry. We measured subjective response to treatment by using the maximum percent improvement over the two hour post treatment period.

3. Statistical Analyses

The spirometric index of objective response to each therapy was prespecified as FEV1 (forced expiratory volume in 1 second).

Drug and placebo effects were assessed with repeated measures analysis of variance. If significant main effects were found, we compared each condition using two-tailed, paired t-tests. For our main outcome measures there were a total of 6 pair-wise comparisons, therefore we used a Bonferonni correction to control Type I error, and only effects with p-values below 0.008 were considered significant. For clarity, we report the actual, uncorrected p-values. The magnitudes of the effects were assessed using Cohen's d, a standardized effect size measure.[8] Cohen's d is the difference between two means in standard deviation units.

The psychometric properties of the subjective measure were examined by using Cronbach's alpha (a measure of internal consistency) to assess reliability, and Kolmogorov–Smirnov tests to assess whether the distributions deviated significantly from normality. Ranges and standard deviations were examined to determine whether

ceiling or floor effects existed and to assess the degree to which respondents used the entire range of the scale.

We also examined reliability of subject response as defined by a 12% improvement in FEV1 to each intervention on at least 2 of 3 occasions (See online Repository Table 4)

4. Statistical Power

The null hypothesis was that all four conditions would show identical improvement (i.e., no effects). Given our sample size of 39 and using a repeated-measures analysis of variance with alpha set at 0.05, we had 97% power to detect a medium-sized (f = .25) main effect (i.e., whether at least one of the four conditions differed from at least one of the other conditions).

Results

1. Results of objective and subjective outcomes

Seven subjects (15%) failed to complete all study visits. Since the study had a within-subjects design and each subject served as his or her own control, our analyses were restricted to the 39 subjects who completed the protocol. We also ran analyses including the partial data of the seven drop-outs and found no substantive change in the results. Similar to the open label screening visit at which subjects' FEV1 improved 21.9%, subjects at the final visit demonstrated a 20% improvement in FEV1 in response to administration of open label albuterol.

1.a. Objective Physiological Outcome

Calculation of Cronbach's alpha indicated that data from the three trials within each of the four conditions (blinded albuterol inhaler, blinded placebo albuterol inhaler, sham acupuncture, and "no treatment" control) were internally consistent, with coefficients ranging from .45 to .85 for FEV_1 and .64 to .86 for subjective improvement. Therefore, to estimate drug and placebo effects, the data from the three trials for each of the four conditions were averaged to produce a single estimate of the effect in each condition.

1.b Subjective patient reported outcome

The psychometric properties of the subjective scale appear to be good. Patients used the full range of the scale for all treatment conditions (ranges were 0 to 9.7 or greater; standard deviations ranged from 2.4 to 2.5). Reliability as indexed by Cronbach's alphas was acceptable to good (0.64-0.83) and comparable to FEV_1 (0.52-0.85). For each of the

three treatment conditions the distribution of subjective responses did not differ significantly from normality.

1.c. Exhaled Nitric Oxygen Data:

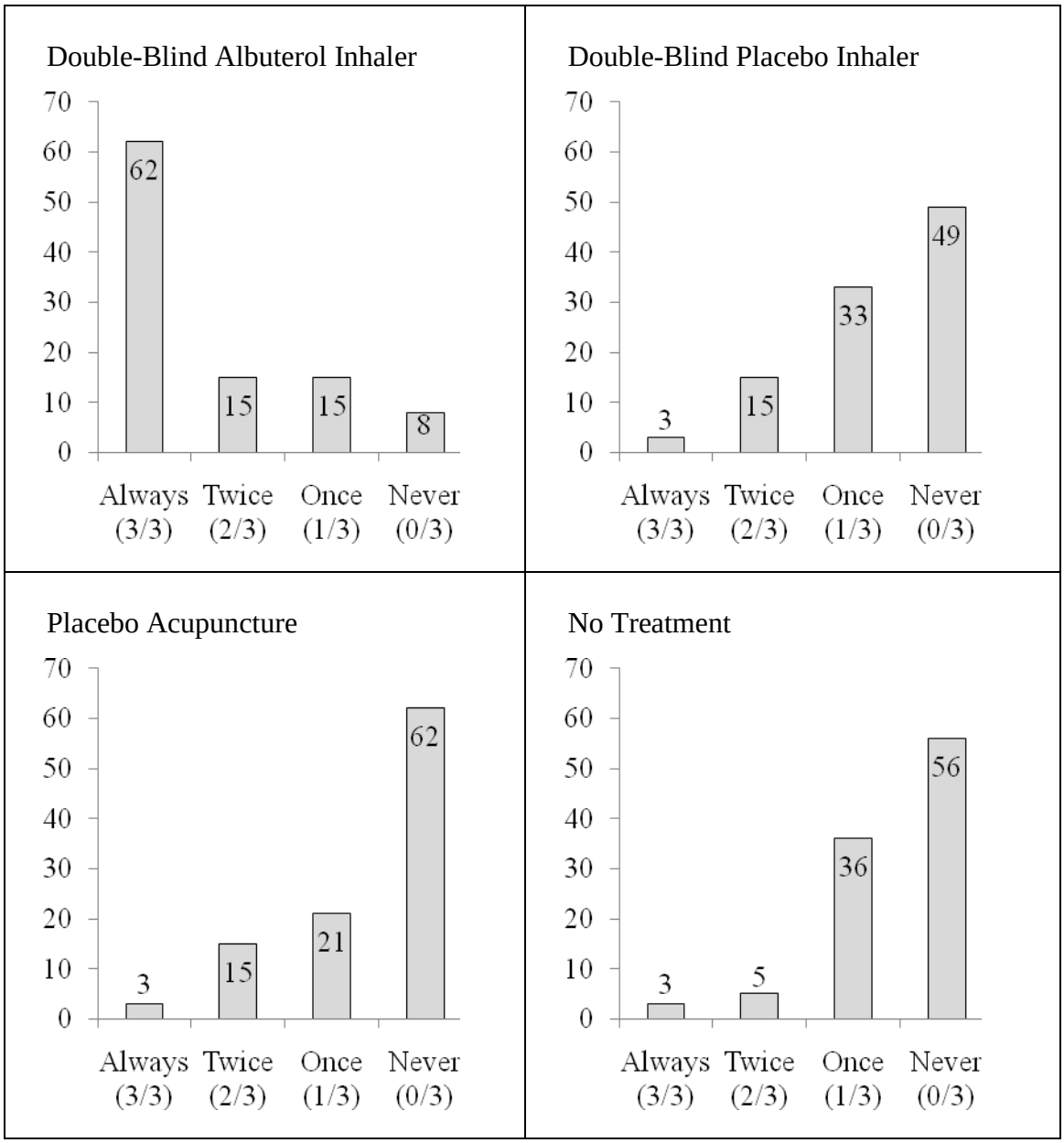
Exhaled NO (F_{ENO}) was measure in at least 32 of 39 subjects at each of the visits, however, only 20 (51%) have data for all time points. Immediately after treatment, F_{ENO} increased in patients treated with double-blind albuterol by 5.9%, whereas patients treated with placebo inhaler, placebo acupuncture, and no treatment had no significant change (see Online repository table 5). At two hours post treatment, as predicted following multiple spirometries, mean F_{ENO} declined following each of the four interventions; nonetheless, treatment with double-blind albuterol resulted in higher F_{ENO} compared with baseline (2.9%) compared to the other interventions, in which subjects had ~6% F_{ENO} decline from baseline.

1. d. Blinding

Treatment credibility was high, and most subjects believed that they had received active treatment (73% for double-blind albuterol; 66% for double-blind placebo inhaler, and 85% for sham acupuncture). The two double-blind conditions did not differ significantly from one another, but sham acupuncture was significantly more credible than both inhaler conditions ($p<.05$). Belief that one has received an active treatment was associated with better subjective outcome (average effect size d=0.71), but not with FEV_1 (average effect size d=0.02).

1. **ONLINE REPOSITORY FIGURE 1**: The percentage of patients who responded physiologically to each intervention with different frequencies

Percent of Patients Who Responded Physiologically (FEV_1 Improvement >12%) with Various Degrees of Reliability.



2. Online Repository Table 1- Inclusion and Exclusion Criteria

Online repository Table 1: Inclusion and Exclusion Criteria

Inclusion Criteria

- Men and women age>or= 18 with a diagnosis of asthma
- Meet American Thoracic Society diagnostic criteria for asthma
- Currently using a stable asthma regimen (no med. changes for 4 weeks)
- Ability to withhold short-acting bronchodilators for 6 hours prior to each visit (see Spirometry description)
- Ability to withhold long-acting bronchodilators for 48 hours prior to each visit (see Spirometry description)
- Presence of reversible airflow obstruction as demonstrated by an improvement in FEV_1 of$\geq$ 12 % following the inhalation of a β-agonist after 10 am. at screening visit .

Exclusion Criteria

- Lung disease other than asthma
- Respiratory tract infection within the last month
- Active tobacco use
- Asthma exacerbation requiring the use of systemic corticosteroids within the past 6 weeks
- Prior experience with acupuncture

Online Repository Table 2: Psychological Variables in study subjects (Personality Assessment Inventory and NEO Personality Inventory)

Personality	
Extraversion	50.9 (9.8)
Neuroticism	49.8 (8.0)
Agreeableness	47.9 (11.0)
Conscientiousness	46.8 (10.0)
Openness	54.2 (9.5)
Psychopathology	
Somatization	49.9 (9.4)
Obsessive-Compulsive	48.8 (6.7)
Interpersonal Sensitivity	48.7 (8.1)
Depression	48.6 (6.4)
Anxiety	45.5 (7.7)
Hostility	46.7 (6.8)
Phobic Anxiety	45.7 (2.0)
Paranoid Ideation	47.9 (8.5)
Psychoticism	47.5 (5.7)
Global Severity Index	47.8 (6.9)

Note. All values are means (SD) except where noted. Personality and psychopathology variables are presented as T-scores, which are standardized scores with a mean of 50 and a standard deviation of 10 in the reference population of normal adults.

*The PAI includes 10 variables and the NEO contains 5 main factors and 30 sub-factors. These measures of personality and psychopathology were not correlated with outcomes.

Online Repository Table 3: Percent of patients who had a >12% increase in FEV_1 according to the treatment administered.

Condition	N	Percent	Group Percent
Drug 1	31/39	79	
Drug 2	31/39	79	77 (drug)
Drug 3	28/39	72	
Placebo 1	12/39	31	
Placebo 2	7/39	18	24 (placebo)
Placebo 3	9/39	23	
Acupuncture 1	8/39	21	
Acupuncture 2	7/39	18	20 (acupuncture)
Acupuncture 3	8/39	21	
No Treat 1	7/38	18	
No Treat 2	9/39	23	18 (no treat)
No Treat 3	5/39	13	

Online Repository Table 4: Reliable Objective Response Rate (FEV≥12% for at least 2 of 3 trials)

Condition	Percent
Double Blind Drug	77
Double Blind Placebo	18
Sham Acupuncture	18
No Treatment	8

Online repository Table 5: Mean (SD) Percent Change in Exhaled Nitric Oxide (FE_{NO})

Condition	Immediately Post Treatment	2 Hours Post Treatment
Albuterol Inhaler	5.9 (12.3)*	2.9 (11.2)**†
Placebo Inhaler	-1.9 (9.2)	-5.9 (8.7)†
Sham Acupuncture	-0.2 (9.7)	-6.2 (8.7)†
No Treatment	-0.7 (10.3)	-5.9 (8.9)†

*$p<0.01$ for differences between genuine Albuterol and all three other conditions
** $p<0.001$ for differences between genuine Albuterol and all three other conditions
† $p<0.03$ for differences between immediately post treatment and 2 hours post treatment following repeated spirometry

Online Supplement References

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