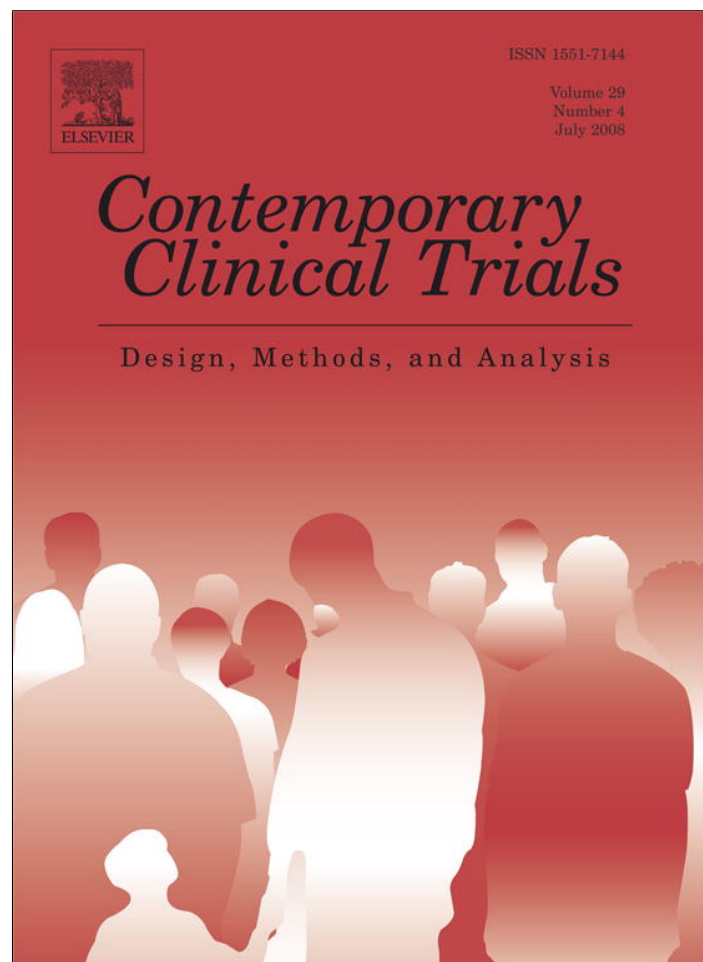


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## Do “placebo responders” exist?

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### Abstract

The placebo effect has been the subject of much controversy. For a scientific investigation of placebo effects to advance it is important to establish whether a placebo response in any particular illness is *reliable* — i.e., if there is a response to a single placebo administration there will also be a placebo response to the repeated administration of a similar placebo in similar conditions. A positive answer would allow more sophisticated clinical trial designs and more precise basic research experiments on the placebo effect. This article reviews experiments that used multiple administrations of placebo to answer the question “do *reliable* placebo responders exist?” This paper also examines the evidence for the existence of a *consistent* placebo responder, i.e. a person who responds to placebo in one situation will respond in another condition or using a different type of placebo ritual. Much of the existing evidence for these two questions was performed before 1967. This early evidence is contradictory, methodologically weak and is sufficiently old to be considered medical history. Since 1969, at least eight experiments exposed asthma patients to multiple administrations of placebo given with deceptive suggestions that the “treatment” was an active medication. While the results of this research are not unequivocal, and may not be equivalent to non-deceptive conditions, this line of inquiry suggests that if a reliable and consistent placebo response exists it could be detected within this population. Finally, this paper proposes one model to rigorously investigate the stability of placebo responses.

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**Keywords:** Placebo effect; Placebo responder; Research design; Clinical trials; Asthma

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### 1. Introduction

Until about 1955, a placebo was an innocuous substance – a “pious fraud” – given to manage difficult patients [1,2]. With the rise of the placebo-controlled randomized controlled trial (RCT), it became evident that the placebo arm of trials often produced significant

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clinical changes [3]. Yet placebo effects remain poorly understood. Recently, sophisticated laboratory studies on very short-term placebo treatment have revealed quantifiable changes in neurotransmitters, hormones, immune regulators and regionally specific brain activity that could influence peripheral disease processes through plausible physiological mechanisms [4–9]. Whether and how these short-term laboratory induced placebo effects apply to research and clinical outcomes over time remains unclear [10,11].

A key challenge for placebo studies is the absence of knowledge concerning whether a placebo effect demonstrated in any trial or experiment is replicable. Within any particular medical condition, are there people who respond more or less reliably when administered a placebo treatment? Are we studying something that is stable? Answers to these questions and the detection and characterization of any such individuals would potentially allow for more efficient RCT designs, a more “personalized” approach in clinical care and more definitive placebo mechanism studies. For example, accurate identification of placebo responders might allow more efficient entry criteria in RCTs and allowed a more precise selection of medications in clinical practice. In basic science research, if people respond inconsistently to a placebo intervention the search for genetic, immunological, or neurological mediators of placebo responses may be extremely difficult and require different modeling assumptions [12]. Advances on all these fronts, would benefit from a better understanding of the stability of a placebo response.

For early pioneers of the RCT, distinguishing placebo responders from non-responders was a major issue [13]. Researchers worried that genuine drug efficacy could be obscured in an experiment with a large number of placebo responders or the optimal dosage of a medication could easily be miscalculated [14]. Then, as now, high placebo response rates in RCTs threatened the detection of an active pharmacological effect [15–18]. The most common method of attempting to detect placebo responders was a retrospective strategy in which baseline demographic, psychosocial, personality, and behavioral variables were correlated with responses in the placebo arm of RCTs [19]. Such analyses continue to this day [20]. While these efforts have been extensive, the conclusion of the most recent reviews of these efforts have been similar: “many variables were identified as being associated with placebo effects, but there was little or no agreement [between trials] about which variables contributed to...the placebo reaction.... [Associations] could not be replicated and they simply disappeared into the wastebasket of history, never to be heard from again.” [21] (cf. [22,23]) These reviews echoed the conclusion of reviews from an earlier era. [24–27].

The failure of these retrospective analyses is likely due to inherent limitations in methodology. One weakness was the inability of these studies to clearly document that the phenomena they measured were, in fact, placebo responses beyond the effects of natural history and regression to the mean. An additional natural history control to distinguish a genuine placebo effect was generally absent. What was called a “placebo effect” could have easily been a mistaken label for spontaneous remission and natural variability, Hawthorne effect, measurement drift or the response to nursing care, bed rest, or other common co-interventions [28]. Ultimately, little clarity has been gleaned with this methodology. Furthermore, by considering a *placebo administration episode* as a cycle of baseline assessment, placebo administration, response, and re-assessment, these retrospective studies rely on a *single* placebo administration from which a subject’s placebo reactivity is inferred. One researcher called making such an inference about a placebo response being more than chance as “near indefensible” [26].

Common forms of statistical representation can also contribute to confusion concerning placebo responses. For example, if 50% of patients on placebo improve, the typical interpretation is that 50% of the patients are placebo responders. Although at first glance this interpretation seems to be perfectly reasonable, Senn has pointed out there are several alternative interpretations [12]. It is possible that 100% of patients respond to placebo 50% of the time implying that all patients are partial placebo responders. If this interpretation were true, there would be no way to distinguish between placebo responders and non-responders. It would only be a matter of chance as to who ended up being identified as a responder in any single trial. This interpretation would explain why it has been so difficult to identify any replicable characteristics that separate placebo responders from non-responders. An additional typical assumption is that the 50% of patients who responded to placebo will *reliably* respond to the placebo, and that, therefore, they must differ in some way from non-responders. Patients who respond to a single placebo administration are usually labeled “placebo responders,” and unfortunately, it is easy to reify this label and assume that they would respond reliably. Another possible interpretation is that some patients may be reliable placebo responders, others may be partial responders, and some may never respond to placebo. The only way to determine which interpretation of placebo responses is correct is to run patients through multiple placebo administrations. This paper will review the few studies that prospectively studied the existence of placebo responders with repeated administrations of

placebo. Some of these experiments were concerned with the *reliability* of placebo response: if there is a response to a placebo administration for a symptom or condition will there be a placebo response to the repeated administration of a similar placebo under similar conditions? Other experiments studied the *consistency* of response: if there is a response to a single placebo administration will there be a response to a different placebo or therapeutic ritual? After examining these experiments, we will present one model for the future investigation of placebo responders.

## 2. Early experiments designed to detect placebo responders

### 2.1. *Lasagna and colleagues (1954) [14]*

To our knowledge, the placebo pioneer team of Lasagna, Mosteller and Beecher at Harvard Medical School performed the first experiment to detect placebo reactors using multiple administration of placebo therapy on the same patient population. In this experiment, 93 patients with severe post-operative pain repeatedly received placebo or morphine in alternating order. Medication or placebo was considered to have produced relief when the patient indicated significant relief of pain (“over 50%”) at both 45 and 90 min after injection. Additional doses of morphine or placebo were administered only if the pain returned. Sixty-nine patients received between two to eight placebo treatments. Of these: ten of the patients (14%) were reliable reactors (i.e., all placebo doses were effective), twenty-one participants (31%) were always non-reactors (i.e., placebo doses were never effective) and thirty-eight (55%) behaved inconsistently (i.e., sometimes placebos worked and sometimes they did not). Using baseline Rorschach tests and qualitative interview, responders, compared to non-responders, were more anxious, self-centered, viewed the hospital care as “wonderful”, had more somatic symptoms, used more cathartics, were “talkers” and were regular churchgoers. Non-responders were described as “far more rigid and emotionally controlled” and “withdrawn and rigidly clinging to critical intellectual processes, less comforted by the care received.” The researchers concluded that placebo responders exist and can be characterized with psychological and behavioral traits.

Confidence in the results of this experiment would be increased if more experimental details were included and one knew the exact number of times placebo was administered and, therefore, allow calculation of the expected number of three-time or four-time placebo responders based on chance. Nonetheless, this ground-

breaking effort launched the prospective inquiry search for reliable placebo responders.

### 2.2. *Wolf and colleagues (1957) [29]*

A rival team of equally famous placebo researchers, originally based at Cornell University Medical School in New York, performed the next experiment designed to examine reliability in placebo response. Thirty-five volunteers were selected who were responsive to the emetic effect of ipecac. Then they were given seven further administrations of ipecac that were preceded by an oral placebo which subjects were told would prevent nausea and vomiting. A failure to develop nausea and/or vomiting was designated as a placebo response. A non-reactor was an individual who consistently had nausea and/or vomiting and a half-reactor was someone who had 3–4 positive responses out of 7 administrations. The team found that placebo response on one occasion did not predict a subsequent response and the more placebo challenges administered, the less reliability was observed. Both inter-individual and intra-individual variations in incidence of placebo response with respect to nausea were no different than the chance curve derived from the binomial equation. Whether a placebo response had predictive value with respect to the likelihood of a future response produced a 50:50 distribution of reactors and non-reactors; when an odd number of tests were analyzed there was a 33:33:33 distribution of reactors, non-reactors and half reactors. About 60% responded to more than half the tests. The last reliable placebo-responding individual disappeared on the seventh trial. The investigators concluded that placebo response was unpredictable.

The interpretation of this ingenious experiment is limited by the fact that subjects were healthy volunteers and the placebo was designed to prevent an induced symptom as opposed to treating a preexisting symptom.

### 2.3. *Batterman (1957) [30]*

Few details are presented in this published abstract report in which 86 patients were repeatedly administered placebo for chronic musculoskeletal pain. The exact number of repeat administrations is not described, but the author reports that 13% of patients always responded and 76% may or may not have responded to different administrations of placebo medication. Response to one administration did not predict response to a second administration of placebo. Unfortunately, such important particulars pertaining to inclusion criteria, number of placebo administrations, definition of

placebo response and actual data are not available in the abstract.

#### 2.4. Joyce (1959) [31]

C.R.B. Joyce, an early British placebo researcher tried a different approach in an explicit follow-up of the Lasagna and Wolf studies. Although his experiment lacked multiple placebo administrations, he tested whether placebo response is prospectively predictable, and therefore, the data is pertinent this discussion. During phase 1, a cohort of fifty-nine medical students, who had previously been given an extensive battery of psychological and personality tests, were given orange juice and told that it “might or might not contain an active substance whose nature (if present) was to be determined by its action.” A 25 symptoms checklist was used as outcome. A placebo reactor was defined as someone who developed two or more symptoms from pre-drug baseline. Responders were more sociable, extravert and enjoyed group activity. In phase two, a different group of fifty-nine medical students were given a similar placebo challenge. The psychological profile of responders in the first group was highly predictive of those who responded in the second group of responders ( $p < 0.005$ ). The author felt that this study confirmed Lasagna’s findings and contradicted Wolf’s findings. Whether measurements of hyper-vigilance in healthy normals after taking the “drug” should be considered a placebo effect is unclear.

#### 2.5. Frey (1961) [32]

One hundred and fifty outpatients in a headache clinic were given identical placebo treatments during three consecutive episodes of what was in the “great majority” of cases “tension headache.” Each subject received placebo and waited in the dispensary for 60 min. A nurse recorded results as complete relief, partial relief or no relief. Twelve patients (18%) reported complete relief from each of the three trials. Thirty-six patients (24%) failed to receive any relief on any of the three trials. The absence of natural history controls, the effects of sitting and waiting, weak outcome measures and poorly defined subjects makes this experiment difficult to interpret.

#### 2.6. Liberman (1967) [33]

Performed by a student of Lasagna, this work was designed to extend Lasagna’s experiment by performing an elaborate, if not daring, set of three interconnected

experiments on pregnant and later postpartum women. The experiments did not test for the existence of reliable placebo responders as much as the existence of consistent placebo responders, that is, whether in a variety of different conditions the same person would repeatedly respond to placebo treatment. Fifty-one pregnant women treated with placebo and an equal number of matched no treatment controls were studied under three conditions: labor, postpartum period and in an experimental pain situation that was explained as being an important clinical procedure. During labor and postpartum, subjects in the placebo “treatment” group were administered subcutaneous injections of saline described as “the best pain killer yet discovered for labor (or postpartum) pains.” The third placebo administration situation is a bit more complex. Before discharge, subjects were told that they needed to undergo a routine “blood vessel” test. The test was actually a procedure for inducing ischemic muscle pain with pain threshold considered the endpoint. In this experimental model of induced pain, following a pre-placebo baseline trial, patients were given a lactose pill and were told that it “contained medicine that acted on healthy blood vessels but not on the diseased blood vessels.” Furthermore, healthy blood vessel, but not diseased blood vessels, would respond to this treatment and allow more blood to enter them and therefore enable the subject to squeeze for a longer time before pain was experienced. In all three situations, it seems that the control group received no treatment. The control group performed the same ischemic pain test without placebo treatment but was simply told that the blood vessel’s health was being assessed. In each of the three circumstances, the placebo group demonstrated significantly greater aggregate relief of pain than the no treatment group ( $p < 0.001$ ). Within individuals, a score of one standard deviation above the mean pain relief score of the control group was considered a placebo response. Three subjects did not respond in any of the three circumstances; twelve responded in one of the three situations, twenty-two responded in two of the three situations, and fifteen responded in all three challenges. According to the statistical assumptions used by Liberman, the observed number (15) of consistent responders is not statistically significant. The author concluded that a placebo response in one situation did not predict a response in another situation and that placebo reactivity is a “potential tendency that can become manifest under the right circumstances in anyone.” From a modern perspective, credibility for this terrifying experiment would be strengthened if the assignment to experiment group had been randomized.

### 2.7. Summary of the pre-1967 placebo responder experiments

The experiments described above were pioneering efforts. The collective evidence of this era is meager, unclear, contradictory and, from a contemporary perspective, methodologically flawed. These studies do not allow for even a tentative answer to the question of whether there are placebo responders in general or in any specific condition. After the Liberman experiment efforts to locate placebo responders seem to discontinue. Undoubtedly, an important reason for the abandonment of this type of experimentation has to do with the introduction and the widespread acceptance of informed consent in the late 1960s [34]. Such experiments would not be possible afterwards. The only exception to this cessation of experimentation using multiple administrations of placebo is a subsequent research agenda of placebo administration paired with “suggestion” in asthma patients which is described below.

### 3. Experiments on placebo responses in asthma patients

Between 1968 and 2003, multiple experiments were performed to test the effects of “suggestion” on asthma patients [35]. Usually, placebo inhalator was given to patients who were deceptively “told” that the placebo was either a bronchodilator or bronchoconstrictor (e.g., placebo allergen). Rooted in a psychosomatic research agenda, these experiments were not designed to test the stability of placebo response. Nonetheless, a close examination of these experiments reveals at least eight experiments that administered multiple episodes of placebo plus different information. More properly considered studies in “placebo-related effects,” these eight experiments, nonetheless, suggestively provide preliminary data on the related questions of whether there might be a reliable or consistent placebo response in asthmatics. Table 1 summarizes these studies.

An examination of Table 1 suggests that the earlier experiments from 1968 to 1986 consistently found a significant number of patients who responded to multiple administrations of placebo plus suggestion with either a reliable placebo-like response (i.e., placebo with similar suggestions produced similar outcomes) or had a consistent response (i.e., placebo with contradictory suggestions produced contradictory responses). From 1987 onwards, the results are less impressive. The only experiment with no treatment controls demonstrates the absence of any placebo response compared to natural history. Interpretation of these studies must be done with

caution: the number of placebo exposures was often only two times and, therefore, insufficient to rule out chance responses, definition of placebo response are inconsistent, the number of inhalations per administration, time between inhalations and number of administrations per session are highly variable and often missing. Some researchers have raised questions regarding whether the inhaled placebo in the earlier studies was genuinely inert [44]. Finally, whether these placebo plus suggestion experiments are relevant to understanding placebo effect without suggestion as is given in RCTs is unclear. Nonetheless, it would seem that asthma might be a valuable illness condition to investigate the reliability and consistency of placebo responses. Our team’s model of one such ongoing experiment with asthma is described below.

### 4. An asthma model for investigating the stability of placebo response

In an effort to investigate placebo responders, our team has recently undertaken an experiment that we hope will provide more reliable evidence of the existence or non-existence of such responders or at least valuable preliminary data. Earlier asthma experiments suggest a reasonable likelihood for finding placebo reactors if they exist. Chronic asthma patients also have the characteristic that withholding regular medications the evening of the day before experimental sessions would induce decrease in lung function and thereby allow volunteers to undergo repeat administration of placebo in multiple sessions. The salient refinements of our experiment are described below.

#### 4.1. Double-blind presentation, inertness and multiple placebo modalities

As placebo issues in clinical trials are our focus, in our ongoing experiment, we deliver the placebo administration in double-blind context that resembles the current standard of clinical research. Therefore, participants are told that they may or may not receive genuine treatment or placebo control. Besides being closer to the object of our interest, this method also has the advantage of being ethically less problematic. The disadvantage of such double-blind administration is that it may result in underestimating potential placebo effects as they might manifest in actual clinic or in experimental models that use deceptive administration [45].

Addressing questions of the placebo inhalant is not inert, our inhalant contains trichlorofluoromethane and dichlorodifluoromethane with lecithin in an unmarked

Table 1  
Acute asthma and inert substance intervention studies

Study, interventions	N	Outcome measures	% subjects with positive response to 2 or more placebo administrations	Natural history control
(Luparello et al., 1968) [36] Placebo allergen, placebo bronchodilator	40 40 controls	Raw, TGV	19/40 48(%) with asthmatic response to placebo; 12/12 100(%) with bronchodilatory effect to placebo Nonasthmatic controls had no deterioration with placebo. Demonstrated stability of placebo response in asthmatics	No
(McFadden, Jr. et al., 1969) [37] Placebo allergen, placebo bronchodilator on more than 1 occasion	29	Raw, TGV	15/29 52(%) with asthmatic response to placebo; 13/29 45(%) had repeated asthmatic response to placebo.	No
(Neild and Cameron, 1985) [38] Placebo bronchodilators and bronchoconstrictors	25	FEV1	10/25 40(%) with decreased FEV1 with placebo+ bronchoconstrictor suggestion; 10/25 40(%) improved with placebo+bronchodilator suggestion Demonstrated reliability of placebo response.	No
(Butler and Steptoe, 1986) [39] Natural history/open-label placebo followed by placebo bronchodilators and bronchoconstrictors	12	Raw, FEV1	12/12 100(%) demonstrated bronchoconstriction with bronchoconstriction suggestion+placebo; but no effect with placebo but no suggestion. Demonstrated consistency of placebo response.	Yes
(Pastorello et al., 1987) [40] Saline and bronchoconstriction suggestion	25	FEV1	11/25 44(%) bronchoconstricted with placebo and negative suggestion; 7/11 had similar response with placebo but no suggestion. Demonstrated placebo effect but absence of suggestion effect	No
(May and Hansen, 1988) [41] Bronchodilator vs. 2 different placebos (saline, air) with bronchodilator suggestion vs. natural history	24	FEV1, FVC	24/24 100(%) of subjects responded significantly to true bronchodilator and to a lesser extent to each of the placebos and to natural history. Demonstrated that placebos may improve lung function, but no difference with natural history, suggesting no true “placebo effect in this cohort.”	Yes
(Isenberg et al., 1992) [42] Placebo with neutral suggestion, bronchoconstriction suggestion and bronchodilator suggestion	33	FEV1, FVC, MMEF	1/33 3(%) responded to placebo bronchodilator;; 0/33 responded to placebo bronchoconstrictor. Demonstrated no placebo effect.	Yes
(Leigh et al., 2003) [43] Placebo bronchoconstrictor and placebo bronchodilator in suggestible and suggestion resistant subjects	17	FEV1	5/8 63(%) in suggestible subgroup bronchoconstricted with placebo and suggestion; 1/9 11(%) in nonsuggestible subgroup. 0/17 bronchodilated. Demonstrated that a suggestible subgroup may respond to bronchoconstrictor placebo stimulus	No

Raw = airway resistance; TGV = thoracic gas volume; PEFr = peak expirator flow rate; FEV1 = forced expiratory volume in the first second; FVC = forced vital capacity; MMEF = maximum midexpiratory flow.

metered-dose inhaler as is standard practice for pharmaceutical industry to insure inert controls in drug development.

The consistency of a placebo response will also be investigated by the inclusion of a second placebo modality to see if a response to one placebo will predict the response to a different placebo. As the second placebo, we have adopted a validated sham acupuncture device which is indistinguishable from regular acupuncture [46–49]. The patient feels and sees the needle pierce their skin but it actually telescopes up the shaft of the needle like a magic sword.

#### 4.2. Controls for natural history, diurnal variation and effects of repeated testing

The entire field of placebo research has been confounded by the lack of sensitivity to the need for controls for natural history and spontaneous remission [10]. Therefore our repeated placebo administrations will have interspersed sessions of “no treatment” controls in which the natural history of the disease over a 2-hour period will be the primary determinant of underlying response. The no treatment controls will be the exact duration of the “intervention” session

and have similar participant research coordinator interaction.

Because of diurnal variation in lung function, all sessions of the study will take place between 10am and 2:30pm [50,51]. Many earlier experiments performed multiple placebo administration on the same day. Because extensive forced breathing in repeated testing can affect lung capacity, our experiment will have only one placebo or treatment modality per session.

#### 4.3. Outcomes and measures of response

The criterion for defining a placebo response is a major issue in any study of placebo. As the criterion for defining “response” decreases, the proportion of positive responses will increase. While many studies have defined placebo response as a >20% increase in FEV1, this study will use a  $\geq 12\%$  increase in FEV1 from baseline (at least 200 cm<sup>3</sup>) measured after the administration of the placebo as the threshold of response. This threshold is identical to that used by the American Thoracic Society [52] to ascertain whether or not an individual is responsive to bronchodilators; it was also chosen because an overly stringent criterion might make a small effect undetectable. We will assess the *reliability* of the placebo response by determining whether response to a single placebo administration predicts response on the two additional administrations of placebo. We will assess the *consistency* of the placebo response by determining whether response in one placebo modality (e.g., inhalant) predicts response in another modality (e.g., acupuncture).

Importantly, as it is an important issue in placebo studies, our experiment also presents the opportunity to compare objectively measured placebo responses (FEV1)

to subjective placebo responses. Therefore, we have included a 10 point subjective scale, anchored with 0=“no improvement at all” and 10=“complete improvement.”

#### 4.4. Testing open-label versus double-blind medication and blinding precautions

The effect of administering open-label medication versus administering the same medication double-blind has been the subject of various studies [53,54]. As all patients in our study will be given genuine albuterol at the intake session to insure reversibility of asthma, the study will have an opportunity to test how “knowing” versus double-blind uncertainty impact on the magnitude of identical medication. To increase statistical power for this comparison, we have inserted a second session of open-label albuterol inhalator at the end of the experiment to obtain a second data point for comparison to the double-blind sessions in the rest of the experiment.

For most of the earlier asthma experiments described above, it is unclear whether researchers were blind. In our experiment, the patients, research coordinator and study physician are blind to all other administrations of albuterol or placebo albuterol besides the first and last sessions, while only the patients are blind to the administration of placebo acupuncture. Double-blind albuterol is the normal situation in RCTs and single blind acupuncture is the normal situation in acupuncture RCTs.

#### 4.5. Overall design

After a baseline visit and treatment with genuine bronchodilator response to test reversability, all subjects undergo 13 additional visits. Before each session, volunteers

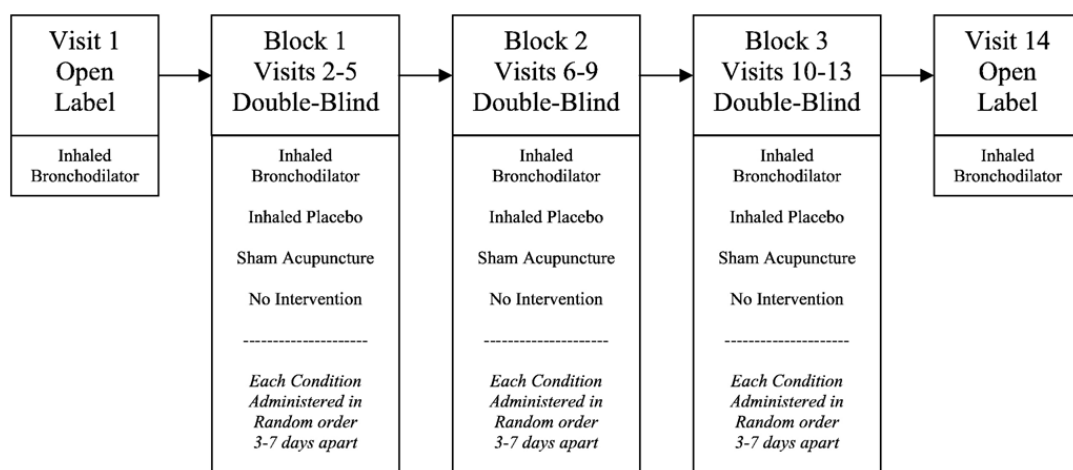


Fig. 1. Overall design.

will be told to withhold medications the night before. After baseline, they will undergo assessment after inhaled placebo (3 times), sham acupuncture (3 times), inhaled genuine bronchodilator (3 times) and no intervention (3 times.) The “interventions” will be administered in a single-block crossover design. (see Fig. 1). To further test the difference of open-label versus double blind, patients will return for a final visit to receive open-label albuterol.

#### 4.6. Statistical considerations

We have little solid evidence on which to base an estimate of effect size. We plan to first run a pilot study with 40 patients, and then use the results from that study to estimate the effect size. With 40 patients, if we find just one reliable placebo responder, this would correspond to an estimated response rate of 2.5% in the population. If the true reliable placebo response rate is lower than 2.5%, we probably will not find any placebo responders. On the other hand, such a low response rate suggests that reliable placebo responders are very rare indeed.

## 5. Conclusion

Previous research on the reliability and consistency of placebo response is contradictory and flawed. Based on an examination of previous experiments of asthma, our team proposes an experiment to further investigate the possibility that reliable and consistent placebo responders exist. Our experimental design addresses many of the shortcomings of previous placebo responder experiments.

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