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The Powerful Placebo Effect: Fact or Fiction?

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ABSTRACT. In 1955, Henry K. Beecher published the classic work entitled "The Powerful Placebo." Since that time, 40 years ago, the placebo effect has been considered a scientific fact. Beecher was the first scientist to quantify the placebo effect. He claimed that in 15 trials with different diseases, 35% of 1082 patients were satisfactorily relieved by a placebo alone. This publication is still the most frequently cited placebo reference.

Recently Beecher's article was reanalyzed with surprising results: In contrast to his claim, no evidence was found of any placebo effect in any of the studies cited by him. There were many other factors that could account for the reported improvements in patients in these trials, but most likely there was no placebo effect whatsoever.

False impressions of placebo effects can be produced in various ways. Spontaneous improvement, fluctuation of symptoms, regression to the mean, additional treatment, conditional switching of placebo treatment, scaling bias, irrelevant response variables, answers of politeness, experimental subordination, conditioned answers, neurotic or psychotic misjudgment, psychosomatic phenomena, misquotation, etc.

These factors are still prevalent in modern placebo literature. The placebo topic seems to invite sloppy methodological thinking. Therefore awareness of Beecher's mistakes and misinterpretations is essential for an appropriate interpretation of current placebo literature. J CLIN EPIDEMIOL 50;12:1311–1318, 1997. © 1997 Elsevier Science Inc.

KEY WORDS. Placebo, placebo effect

Placebo effects have gained great popularity. Within the last three years hardly any major medical journal failed to have publications about placebo effects and their scientific basis. The tradition of placebo research goes back to the fifties. It was in 1955 that Henry K. Beecher, with his famous and seminal article "The Powerful Placebo" [1], was the first author to quantify the effects of placebos in a variety of diseases. He claimed that the symptoms of 35% of 1082 patients in 15 studies [2–16] were satisfactorily relieved by placebos alone [1]. Today placebos are supposed to be effective in almost every disease, and estimates of the extent of the placebo effect even go far beyond Beecher's 35% [17–20].

This paper fundamentally questions the claimed extent of the placebo effect. A reanalysis of placebo literature was carried out, with surprising results: A wide range of errors was found in the placebo literature, which produced false impressions of placebo effects.

To illustrate these errors it is most appropriate to refer to the classic "The Powerful Placebo" [1] itself, because it is still the most frequently cited paper on placebo and because its mistakes are still prevalent in placebo literature today (as far as we can judge from 800 articles on the placebo effect we have analyzed [21,22]). In the following article, the results of the analysis of the 15 trials reported in Beecher's article are described. The analysis is based on two questions: 1. Is the existence of the placebo effect demonstrated in those 15 trials that Beecher had surveyed in "The Powerful Placebo"? 2. If not, what are the factors that can create the false impression of a placebo effect?

DEFINITION AND METHODS

It seems easy to define placebos: They are imitations of specific treatments, with the absence of the specific therapeutic constituents. However, defining placebos is a very controversial topic [22–24]. Gøtzsche even concluded, "The placebo concept as presently used cannot be defined in a logically consistent way and leads to contradictions" [25]. From reading Beecher's own article, he refers to "pharmacologically inert substances" [1], the administration of which he considers can have "real therapeutic effects" [1]. Based on this, the criteria for acknowledging a placebo *effect* taken for this present paper are as follows: (1) A *placebo* had to be given. (2) The event had to be an *effect* of the placebo treatment, i.e., the event would not have happened without placebo administration. (3) The event had to be relevant for the disease or symptom, i.e., it had to be a *therapeutic* event.

Besides these three criteria there were no other prede-

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fined criteria for the analysis. Basic medical knowledge and common sense were the only scientific tools.

RESULT

For 14 out of the 15 trial publications [2–16] detailed analysis was possible. (One publication [4] did not give account of the study design.) The overall result was that for none of these trials was there any reason to assume the existence of the slightest placebo effect. These studies were placebo-controlled drug trials. Although they were not carried out in order to investigate placebo effects, Beecher retrospectively attributed the improvements in the placebo groups to *effects* of the placebo administration. However, on the basis of the published data, in all of these trials the reported outcome in the placebo groups can be fully, plausibly, and easily explained *without* presuming any therapeutic placebo effect. The published data of these trials make it quite obvious that there were a variety of reasons for the reported results, such as spontaneous improvements, additional treatments, methodological artifacts, etc. In some of the original trial publications even the authors themselves had explicitly written that there were *no* placebo effects.

Beecher completely neglected all obvious reasons for the outcome in the placebo groups, simply calling the reported results "real therapeutic effects" of placebo administration. Thus, he totally misinterpreted the trials.

Factors that have caused false impressions of placebo effects—not only in Beecher's but in other publications as well—are listed in Table 1. Most of these factors are relevant in the 15 studies surveyed by Beecher; their distribution is shown in Table 2 [1–16,21].

Beecher's "The Powerful Placebo"—presenting a quantitative "proof" of the existence of real therapeutic placebo effects—created a cognitive framework for further placebo research in which all kinds of phenomena were registered as therapeutic placebo effects in a rather uncritical fashion (further details see [21,22]). Therefore, in order to avoid such obvious misinterpretations, it is important to know those factors that can create illusions of placebo effects. They will be described in the following. Examples will be taken from Beecher's "The Powerful Placebo"; for further illustration a few examples will be taken from a similarly classic German placebo survey [17].

TABLE 1. Factors that can cause the false impression of a placebo effect

Natural course of a disease
Spontaneous improvement
Fluctuation of symptoms
Regression to the mean
Habituation
Additional treatment
Observer bias
Conditional switching of treatment
Scaling bias
Poor definition of drug efficacy
Irrelevant response variables
Subsiding toxic effect of previous medication
Patient bias
Answer of politeness and experimental subordination
Conditioned answers
Neurotic or psychotic misjudgment
No placebo given at all
Psychotherapy
Psychosomatic phenomena
Voodoo medicine
Uncritical reporting of anecdotes
Misquotation
False assumption of toxic placebo effects created by
Everyday symptoms
Misquotation
Persistence of symptoms

FACTORS THAT CAN CREATE FALSE IMPRESSIONS OF PLACEBO EFFECTS

Spontaneous Improvement

Spontaneous improvement of a disease does not occur as a result of a placebo administration; it is *not* an *effect* of a placebo. This often seems to be disregarded in placebo literature.

In a placebo-controlled drug trial on acute common cold, described as mild and of short duration, 35% of the patients receiving placebos felt better within 6 days (2 days after the onset of placebo administration) [2] Beecher interpreted these improvements as an effect of the placebo administration [1]. However, he did not consider that many patients with a mild common cold improve spontaneously within 6 days (as already pointed out in the original publication [2]).

Other examples: Four [8,9,12,14] of the trials in Beecher's list evaluated treatment of post-operative pain. Reanalyzing these trials, it was possible in two [8,9] of these studies to determine the spontaneous diminishing of postoperative pain on the basis of published data on the decrease of patients' demand for analgesics. This diminishing rate was equal to that of Beecher's claimed "placebo effect" [21]. Therefore, there is no reason to assume a placebo effect.

Spontaneous improvement was a major factor in Beecher's misinterpretation of 10 of the 15 trials. This error is wide-spread in the placebo literature.

Fluctuation of Symptoms

In chronic diseases (or with chronic pain [26,27]) *fluctuation of symptoms* should be taken into account. Patients feel better one day and worse the next. Therefore, looking at a number of chronically ill patients, one will simply *always* see some patients improving. Because of this, it is a mistake to forget to mention the rate of deterioration, and only report the rate of improvement and call the latter a placebo "effect."

For example, Beecher referred to patients with diseases

TABLE 2. Factors that created the illusion of a placebo effect in H. K. Beecher's study list (quoted from [21])

	Study [see references]														
	[2]	[3]	[4]	[5]	[6]	[7]	[8]	[9]	[10]	[11]	[12]	[13]	[14]	[15]	[16]
Percent of patients who were "satisfactorily relieved by a placebo," according to Beecher [1]	35	38	52	58	26	38	21	26	31	37	26–40	30	15–53	36–43	30
Factors creating illusions of placebo effect															
Spontaneous improvement	x	x		x	x		x	x	x		x	x	x		
Spontaneous fluctuation of symptoms		x			x	x		x				x			
Conditional switching of treatment	x	x				x			x	x	x				
Scaling bias	x	x				x									
Additional treatment	x				x										
Irrelevant response variables					x	x									x
Answer of politeness										x	x		x		
Conditioned answers											x		x		
Neurotic or psychotic misjudgment												x			
Misquotation			x	x		x		x	x	x	x	x	x	x	
Everyday symptoms misinterpreted as placebo side effects												x			x
Habituation				x						x					
Poor definition of drug efficacy					x	x									x
Subsiding toxic effect of previous medication								x							x
Demonstration of placebo effect?	No	No	/[a]	No	No	No	No	No	No	No	No	No	No	No	No

[a]The publication [4] gives no account of the study design.

such as ulcer, migraine, muscle tension, or headache who suffered from anxiety and tension and were treated for eight 2-week periods alternately with mephenesin and placebo [13]. Beecher claimed a placebo effect of 30% since "roughly" 20–30% of the patients improved. However, 10–20% of the patients deteriorated. As can be seen in a published figure, there was only a net improvement of 5–10% [21]. This seems a rather low rate, considering the observation period (16 weeks), the kind of diseases (ulcer, muscle tension, headache, etc.) and possible improvement through the intermediate mephenesin treatment. Therefore, there was no reason to assume any placebo effect. (Besides, no information about patient compliance was supplied in the publication, and it was not ruled out that patients had other medical support.)

Neglecting spontaneous fluctuations of symptoms was the main reason why Beecher also misinterpreted three other trials [3,6,7]. This is a very common mistake also in other literature about placebos: A 20% placebo effect is claimed [17] for a placebo-controlled drug trial on patients with angina pectoris. However, in the same trial, 72% [28] of the placebo-treated patients deteriorated.

A 21% placebo effect is claimed [17] for a trial on cerebral infarction, because 21% of the patients improved in the placebo-group. However, in that trial [29], 53% of the patients on placebo died, even though every patient received the best supportive medical care. (Of course, neither the improvement of 21%, nor the death of 53% of the patients can be reasonably attributed to placebo administration.)

Spontaneous improvement of diseases and the spontaneous fluctuation of symptoms are special forms of *regression to the mean*, i.e., the tendency of extreme values to move closer to the average on repeated measurement. In their interesting article, "How much of the placebo 'effect' is really statistical regression?" McDonald *et al.* [30] have argued, that "most improvements attributed to the placebo effect are actually instances of statistical regression."

Additional Treatment

So-called placebo effects often occur under *additional* treatment. Of course there is no justification to call such improvements a "placebo effect."

In one of the angina pectoris trials in Beecher's list [6] the placebo group additionally received nitrates. In another trial, concerning the common cold [2], the patients were allowed to take rest, hot baths, gargles, diets, etc.

Many other examples can be found in the literature about placebo effects. For instance, a study [31] supposedly shows placebo effects in irritable colon treatment [17], but all patients had been put on a special diet. In another study [32], taken as a show case for placebo effects in alcoholism [17], patients in the placebo group received specialized medical and psychosocial support.

Conditional Switching of Treatment

In some of the trials in Beecher's list the "placebo effect" was further amplified by selecting patients in the following manner: When the patients felt well, they received a pla-

cebo; when they felt worse, they were switched to active treatment, or they were excluded from evaluation until they felt better again.

In a study on angina pectoris [3], patients got placebos as long as they only had a few episodes of angina; when the episodes increased, they received one of the test drugs. Thus good periods were selected for placebo treatment, and bad periods were selected for drug treatment. Consequently, the extent of the placebo effect was grossly overestimated. Similarly in one of the trials concerning treatment of postoperative pain [12], patients were only included when they had already improved to the degree that they could take oral medication. When patients got worse again (pain increase, regurgitation, etc.), they were excluded from evaluation until they improved again.

Scaling Bias

In three of Beecher's trials [2,3,7] there were false augmentations of placebo effects due to asymmetrical measurement scales [21]. The scales included two or more categories for improvement, and only one or even none for deterioration. Thus the scales tempted patients to falsely give too many positive reports.

Irrelevant or Questionable Response Variables

Immense placebo effects can be claimed when they are based on response variables which are irrelevant for the condition in question [21]:

There is the claim of a 73% placebo effect in multiple sclerosis [17]. The facts in the original publication [33] were that no objective change in the neurological condition was found in any patient on placebo, yet 73% of the patients had the subjective feeling of increased euphoria, strength, and agility. However, euphoria is itself a symptom of multiple sclerosis; therefore an increase of euphoria is not necessarily a sign of improvement. Spontaneous variation of euphoric and optimistic answers are typical for this disease and therefore are inappropriate response variables for demonstrating placebo effects.

Supposedly there is a 61% placebo effect in hypertension [17]. The facts in the original trial [34] were that there was *no* significant change in blood pressure under placebo, but 61% of the patients subjectively felt better. However, all patients had first received veratrum, which caused severe toxic symptoms in 64% of the patients. It was then substituted by placebos. Therefore the relief of symptoms in 61% of placebo-treated patients can be explained by the cessation of veratrum toxicity [21]. There is no reason to assume any placebo effect.

Answers of Politeness and Experimental Subordination

In one of the trials on postoperative pain [8] the authors discuss the "exceedingly difficult" criteria of pain relief. They had observed that patients often claimed pain relief in contrast to the physician's impression. This observation is only peripherally related to the trials surveyed by Beecher, but it is of great importance in many other placebo reports [22]. The issue was recently described by Roberts [35]: "The word 'placebo' means 'to please' but this applies to both the patient and the doctor. For example, patients may report positive outcomes to their physicians out of a need to 'be polite' to them." The same issue was addressed by Sackett [36]: "Finally, when the patient is grateful for clinician's time and effort in trying to help them, this gratitude (plus simple good manners) often is reflected in an exaggeration of the benefits of the latest prescription when they are asked 'Did that medicine help you?' "

The same phenomenon was called a *verbal* (in contrast to a *real* therapeutic) placebo effect by Kiene [37]. He also mentioned the phenomenon of *experimental subordination*, i.e., in an experiment the subject says what he thinks he is expected to say, rather than what he really observes or experiences [37]. Similar phenomena have been described by several other authors [38–41].

To differentiate polite answers or experimental subordination from *true therapeutic* placebo effects and to develop appropriate methods for this differentiation [22] is a key issue in placebo research.

Conditioned Answers

It seems difficult to differentiate therapeutic placebo effects and conditioned effects. Numerous authors closely associate them or even presume that conditioning is the basic constituent of placebo effects [42–46]. However, a differentiation is necessary. Conditioned effects need *specific* presuppositions: First a specific unconditioned stimulus and second a specific setting, which is a very close temporal pairing of the unconditioned and the conditioned stimulus. In many instances, conditioning even seems to work only when it superimposes biological rhythms. These specific presuppositions are usually not present in clinical placebo situations.

Since Pavlov, many experiments on drug conditioned responses in animals were carried out. But from these experiments one cannot conclude that *healing* or a real *therapeutic* drug effect also can be provoked as a conditioned reflex. Surely, in cancer patients nausea and vomiting can be conditioned by repeated chemotherapy. But this does not mean that tumor remissions can be conditioned as well. Unfortunately, it is just the other way round: While conditioned vomiting often increases during chemotherapy cycles, there is generally a decrease in the therapeutic sensitivity of the tumor.

In fact, clinical experience contradicts the assumption that healing can be conditioned. Episodes of chronic disease are usually more difficult to treat than the acute or first manifestation of an illness, even if this first manifestation has been treated successfully. (Classical conditioning paradigm

would predict just the opposite.) Moreover, there are many severe symptoms that are treated effectively by regular and repeated drug administration. These therapeutic settings are similar to conditional settings, and therefore should be adequate for the conditioning of therapeutic effects. Yet when interrupting such regular therapies, a rapid deterioration of patients is observed in practice.

Nevertheless, conditioning may be important when giving placebos, in that it can produce answers of politeness, verbal placebo effects, and experimental subordination rather than effecting a true placebo effect. This realm of communication seems far more susceptible to influences such as conditioning than the realm of effective healing. It is easier to provoke such communicative and behavioral reactions than true therapeutic placebo effects. This seems to have happened in one of the pain trials [14] in Beecher's list. It had a typical conditioning setting: Morphine and placebo were either alternated, or series of morphine administrations were interrupted by placebos. In this setting the "placebo effect" decreased after repeated placebo administration. One can find an easy explanation for this decrease, because it was just like in Pavlov's classic experiments. When, in Pavlov's experiments, the ringing of the bell repeatedly was not combined with real food, the salivation decreased. Similarly, when in those patients the drug application ("ringing of the bell") was not combined repeatedly with real pain relief ("food"), the patients' positive answers ("salivation") decreased. This means that the patients gradually recognized that they were receiving inactive treatments, and that only *verbal* placebo effects had been conditioned, *not* real ones [21]. A key issue when judging placebo effects is to decide whether a patient's report is true or not.

In an example of a crossover placebo-controlled study on hypertension, a conditioned reduction of blood pressure was shown, however, it was short term (a few days). Notably, when placebos were given as first treatment within this crossover design, no antihypertensive effect occurred, although 83% of the patients had previously been treated with antihypertensive remedies [47]. Thus, in this trial only a short-term conditioned effect occurred, due to the specific conditioning setting, while there was *no* placebo effect. These findings concur with several trials on placebo in hypertension [48–51]; they did not show any placebo effect either.

Neurotic or Psychotic Misjudgment

The reliability of a patient's report is often particularly difficult to assess in neurotic or psychotic disturbances [21]. Here the placebo literature offers fascinating stories [52]. However, one should not forget that a common feature in psychosis or neurosis is disturbed interpretation of reality. Therefore one clearly has to differentiate between a psychotic or neurotic misjudgment on the one hand, and a correct observation of a therapeutic effect on the other hand. (This differentiation is difficult, but not impossible; in fact, it is the psychiatrist's daily work.) Neurotic or psychotic misjudgments can hardly give any valid evidence for the existence of placebo effects.

No Placebo Given at All

There is a class of anecdotal reports in the placebo literature, which have nothing to do with placebos, because no placebos were given at all [21].

The purpose of these anecdotes is to demonstrate the possible power of "nonspecific" causes. Beecher himself reported adventurous episodes from the voodoo culture, when supposedly dying people recovered immediately, or when magic rituals brought about the death of apparently healthy people [53].

Another classic example is an anecdote in Stewart Wolf's well known "The Pharmacology of Placebos" [54]: A woman with a gastric ulcer could not respond with gastric acid production during provocative tests with even the most powerful secretory drugs. Yet, immediate acid secretion occurred when she was asked about her husband who, as she had just recently discovered, had been sexually abusing her 12-year-old daughter. Wolf used this story to demonstrate the possible range of placebo effectiveness. However, this is misleading. This was an example of a psychosomatic effect, not the effect of placebo application. The example does not show that the mere ritual of giving a pill can be equated with the effect of discovering the sexual abuse of one's daughter by one's husband.

Uncritical Reporting of Anecdotes

One needs to be cautious about claims of placebo effects not only in clinical trials, but also in case reports. While most scientists are reasonably skeptical regarding therapeutic benefits from drugs, they welcome reports about placebo effects with uncritical enthusiasm [55]. For example, Beecher demonstrates the power of nonspecific effects by the following story [53]: A middle-aged woman underwent surgical exploration because of cancer, which was then found to be inoperable. When she had recovered from anesthesia, one of her relatives told her the truth about her illness. Within the next hour the woman went into cardiovascular shock and died after a few hours.

This story, however, does not testify for nonspecific effects. Before diagnosing such a mysterious "placebo" death, every rational doctor must first rule out the most likely causes: postoperative complications, such as bleeding or pulmonary embolism. These are frequent hazards after operations and in cancer patients.

Many such uncritical placebo anecdotes, although impressive, come to nothing when they are looked at a little closer [21].

Misquotation

A particular problem of placebo literature seems to be that of misquotations. An example is Beecher's claim that in a study of antitussive agents [15] there was a placebo effect in 36% of 22 patients and in 43% of another 22 patients. However, the actual result was, that under *none* of the placebo administrations could any significant change be demonstrated. Besides, there were no 22 placebo-treated patients (the groups were much smaller), and there were no reports about any 36% or 43% of patients. Thus, Beecher's quotation was wrong (which is amazing, as Beecher himself had been one of the authors of the original publication).

Beecher misquoted 10 of the 15 trials listed in "The Powerful Placebo." He sometimes inflated the percentage or the number of patients, or he cited as a percentage of patients what in the original publications is referred to as something completely different, such as the number of pills given, the percentage of days treated, the amount of gas applied in an experimental setting or the frequency of coughs after irritating a patient [21]. The main effects of these errors were false inflations of the alleged placebo effect. A multitude of misquotations can also be found in other placebo literature [21].

False Assumptions of Toxic Placebo Effects

Beecher did not only write about "real therapeutic effects" of placebo administration; he also wrote about "toxic and other side-effects of placebos." He states that in various trials there had been 35 different toxic effects of placebos such as dry mouth, nausea, headache, drowsiness, warm glow, fatigue, and sleep. The frequency ranged from 8% to 50%. For this, Beecher did not quote any references.

When judging toxic placebo effects one needs to take into account the studies by Green [57] and by Reidenberg *et al.* [58]. They demonstrated that many people experience *everyday symptoms* such as dry mouth, headache, drowsiness, fatigue, etc. The frequency of these symptoms is similar to the frequency of Beecher's so-called "placebo side-effects." Therefore, it is very likely that these everyday symptoms are documented in a trial situation and are then misinterpreted as "side-effects" of the placebos.

With respect to "toxic placebo effects," one always has to consider the possibility of misquotations. In one of the publications in Beecher's trial list, the authors [13] reported an impressive finding that 61% of the placebo patients in a streptomycin trial showed the specific toxic effects of streptomycin, including high-tone and low-tone hearing loss, eosinophilia, and impairment of urea clearance. This remarkable placebo toxicity has been passed on in the medical literature. However, going back to the original publication [56] one will find that *none* of the patients in the streptomycin trial ever received a placebo.

Finally, symptoms are called "side effects" of placebo treatment, only because they do not disappear or because they get worse [21]. For example, in a trial on chronic pain 13% of the patients in the placebo group improved, and 20% deteriorated. While the improvement was interpreted as a therapeutic placebo effect, the deterioration was interpreted as a *toxic* placebo effect [19,59].

DISCUSSION

Beecher's "The Powerful Placebo," published in 1955, has been a seminal and most influential paper. It is still the most frequently cited placebo reference. This is amazing, as none of the original trials cited by Beecher gave grounds to assume the existence of placebo effects. The reanalysis of a similar classic German placebo survey [17] gave the same results. No placebo effects could be found [21].

The conceptual and methodological mistakes of Beecher's classic paper are still prevalent today. Although some modern experimental placebo research is of better methodological quality, a valid demonstration of therapeutic placebo effects still appears lacking. Having analyzed a total of 800 articles on placebo, we have not found any reliable demonstration of the existence of placebo effects. (In bronchial asthma effects of suggestion are documented under experimental conditions. This, however, does not imply the existence of an efficacious placebo therapy of bronchial asthma [22]).

Comparing placebo-treated and untreated patients might be a valid method for investigating placebo effects. (In one of the trials [5] of Beecher's list there was an untreated control group; it showed the same result as the placebo group.) As these trials, however, do not control for factors such as answers of politeness, experimental subordination and additional treatment they can create false positive results. For instance, Ernst and Resch [60] systematically collected trials that included both a placebo-treated and an untreated group. They found four trials that showed superior outcomes in the placebo groups. The best trials were two 5-arm randomized trials on ultrasound treatment of postoperative swelling. As there were better results in the placebo group (i.e., turned off ultrasound apparatus), than in the untreated groups [61,62] the results were categorized as "true" and "substantial" placebo effects [60]. However, in the placebo groups, a coupling cream was also applied, the humidity and cooling effect of which possibly reduced the postoperative swelling. Consequently, the existence of a placebo effect is questionable in these trials, too. A possibility to do placebo research lies within balanced study designs [63,64] (2×2 factorial designs: verum vs. placebo, strong vs. weak suggestion of efficacy). However, variations of outcome do not indicate true therapeutic placebo effects as long as experimental subordination has not been ruled out [37].

There can be no doubt that the extent and frequency of placebo effects as published in most of the literature are gross exaggerations. Some placebo experts have had some awareness of these issues. For example, Shapiro and Shapiro

[65] wrote: "In our opinion, the belief that placebos and psychological factors have a specific and clinically meaningful effect on physical illness is not supported by a critical, data-oriented review of the literature." Even more drastically, Roberts [35] said: "The so-called placebo effect is a myth born of misperception, misunderstanding, mystery and hope." However, these comments remained isolated even in the Shapiros' and Robert's own publications.

Undoubtedly, psychosomatic effects exist. Hence, clear differentiation between placebo and non-placebo components in therapeutical settings [22] is essential for valid placebo research and for research in complementary medicine. Many factors and phenomena have been summed up under the terms "placebo" and "placebo effect," without being *placebos* or *effects* of placebo administrations. Those factors and phenomena were taken as evidence of "true therapeutic placebo effects," although they are not. Thus, The Powerful Placebo turns out to be a fiction.

One might consider to substitute the term "placebo effect" by the term "non-specific effects." Changing of words, however, does not change the situation that the existence of therapeutic effects of placebo administration seems questionable. Besides, as Peek [66] and Grünbaum [67] have already pointed out, there is no such thing as "non-specific effects." The term is a *contradictio in adjecto*: a contradiction in itself.

Finally, these factors that can create false impressions of placebo effects might seem to be compelling reasons for randomization and blinding. However, analyses indicate that these factors are not necessarily distributed equally in drug and control groups, thus challenging the validity of randomized double-blind trials [37,68–70]. This issue needs further investigation.

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References

1. Beecher HK. The powerful placebo. **J Am Med Assoc** 1955; 159(17): 1602–1606.
2. Diehl HS. Medicinal treatment of the common cold. **J Am Med Assoc** 1953; 101: 2042–2049.
3. Evans W, Hoyle C. The comparative value of drugs used in the continuous treatment of angina pectoris. **Quart J Med** 1933; 7: 311–338.
4. Jellinek EM. Clinical tests on comparative effectiveness of analgesic drugs. **Biometrics** 1946; 2(5): 87–91.
5. Gay LN, Carliner PE. The prevention and treatment of motion sickness. **Bull Johns Hopkins Hosp** 1949; 84: 470–487.
6. Travell J, Rinzler SH, Bakst H, Benjamin ZH, Bobb A. Comparison of effects of alpha-tocopherol and a matching placebo on chest pain in patients with heart disease. **Ann New York Acad Sci** 1949; 52: 345–353.
7. Greiner Th, Gold H, Cattell M, Travell J, *et al.* A method for the evaluation of the effects of drugs on cardiac pain in patients with angina of effort. A study of khellin (visammin). **Am J Med** 1950; 9: 143–155.
8. Keats AS, Beecher HK. Pain relief with hypnotic doses of barbiturates and a hypothesis. **J Pharmacol Exp Ther** 1950; 100: 1–13.
9. Keats AS, D'Alessandro GL, Beecher HK. A controlled study of pain relief by intravenous procaine. **J Am Med Assoc** 1951; 147: 1761–1763.
10. Beecher HK, Deffer PA, Fink FE, Sullivan DB. Field use of methadone and levo-iso-methadone in a combat zone. **U S Armed Forces Med J** 1951; 2: 1269–1276.
11. Hillis BR. The assessment of cough-suppressing drugs. **Lancet** 1952; June 21: 1230–1235.
12. Beecher HK, Keats AS, Mosteller F, Lasagna L. The effectiveness of oral analgesics (morphine, codeine, acetylsalicylic acid) and the problem of placebo "reactors" and "non-reactors." **J Pharmacol & Exper Therap** 1953; 109: 393–400.
13. Wolf S, Pinsky RH. Effects of placebo administration and the occurrence of toxic reactions. **J Am Med Assoc** 1954; 155: 339–341.
14. Lasagna L, Mosteller F, Felsinger JM, Beecher HK. A study of the placebo response. **Am J Med** 1954; 16: 770–779.
15. Gravenstein JS, Devloo RA, Beecher HK. Effect of antitussive agents on experimental and pathological cough in man. **J Appl Physiol** 1954; 7: 119–139.
16. Lasagna L, Felsinger JM, Beecher HK. Drug-induced mood changes in man. 1. Observations on healthy subjects, chronically ill patients, and "postaddicts." **J Am Med Assoc** 1955; 157(12): 1006–1020.
17. Netter P, Classen W, Feingold E. Das Placeboproblem. In: Dölle W, Müller-Oerlinghausen B, Schwabe U, Eds. **Grundlagen der Arzneimitteltherapie–Entwicklung, Beurteilung und Anwendung von Arzneimitteln.** Mannheim, Wien, Zürich: Wissenschaftsverlag; 1986: 355–366.
18. Roberts AH, Kewman DG, Mercier L, Hovell M. The power of nonspecific effects in healing: Implications for psychosocial and biological treatments. **Clin Psychol Rev** 1993; 13: 375–91.
19. Turner JA, Deyo RA, Loeser JD, Von Korff M, Fordyce WE. The importance of placebo effects in pain treatment and research. **J Am Med Assoc** 1994; 271(20): 1609–1614.
20. Bodem SH. Bedeutung der Placebowirkung in der praktischen Arzneitherapie. **Pharm Ztg** 1994; 139(51/52): 9–19.
21. Kienle GS. Der *sogenannte* Placeboeffekt; Illusion, Fakten, Realität. Stuttgart, New York: Schattauer Verlag GmbH; 1995.
22. Kienle GS, Kiene H. Placebo effect and placebo concept: A critical methodological and conceptual analysis of reports on the magnitude of the placebo effect. **Altern Ther Health Med** 1996; 2(6): 39–54. [Reprint from: Kienle GS, Kiene H. Placeboeffekt und Placebokonzept—eine kritische methodologische und konzeptionelle Analyse von Angaben zum Ausmaß des Placeboeffekts. **Forsch Komplementärmed** 1996; 3: 121–138.]
23. White L, Tursky B, Schwartz GE, Eds. **Placebo—Theory, Research, and Mechanisms.** New York, London: Guilford Press; 1985.
24. Hornung J. Was ist ein Placebo? Die Bedeutung einer korrekten Definition für die klinische Forschung. **Forsch Komplementärmed** 1994; 1: 160–165.
25. Gøtzsche PC. Is there logic in the placebo? **Lancet** 1994; 344: 925–926.
26. Whitney CW, Von Korff M. Regression to the mean in treated versus untreated chronic pain. **Pain** 1992; 50: 281–285.
27. Deyo RA. Practice variations, treatment fads, rising disability. **Spine** 1993; 18(15): 2153–2162.

28. LeRoy GV. The effectiveness of the xanthine drugs in the treatment of angina pectoris. **J Am Med Assoc** 1941; 116(10): 921–925.
29. Dyken M, White PT. Evaluation of cortisone in the treatment of cerebral infarction. **J Am Med Assoc** 1956; 162(17): 1531–1534.
30. McDonald C, Mazzuca S, McCabe G. How much of the placebo 'effect' is really statistical regression? **Stat Med** 1983; 2: 417–427.
31. Lichstein J, DeCosta Mayer J, Hauch EW. Efficacy of methantheline (banthine) bromide in therapy of the unstable colon. **J Am Med Assoc** 1955; June 25: 634–637.
32. Wells RE. Use of reserpine (Serpasil) in the management of chronic alcoholism. **J Am Med Assoc** 1957; 163(6): 426–429.
33. Blomberg LH. Treatment of disseminated sclerosis with active and inactive drugs. **Lancet** 1957; 1: 431–432.
34. Coe WS, Best MM, Kinsman JM. Veratrum viride in the treatment of hypertensive vascular disease. **J Am Med Assoc** 1950; 143(1): 5–7.
35. Roberts AH. The powerful placebo revisited: The magnitude of nonspecific effects. **Mind/Body Medicine** 1995; March; 1–10.
36. Sackett DL. Randomized trials in individual patients. In: Antes G, Edler L, Holle R, Köpcke W, Lorenz R, Windeler J, Eds. **Biometrie und unkonventionelle Medizin.** Münster–Hiltrup: Landwirtschaftsverlag GmbH; 1995: pp. 19–33.
37. Kiene H. A critique of the double-blind clinical trial. Parts 1 + 2. **Altern Ther Health Med** 1996; 2(1): 74–80 and 1996; 2(2): 59–64. [Reprint from: Kiene H. **Kritik der klinischen Doppelblindstudie. MMW-Taschenbuch.** München: MMW Medizin; 1993: 35.]
38. Barber TX. The effects of "hypnosis" on pain. **Psychosom Med** 1963; 25: 303–333.
39. Clark WC. Sensory-decision theory analysis of the effect on the criterion for pain and thermal sensitivity. **J Abnorm Psychol** 1969; 74(3): 363–371.
40. Fordyce WE, Lansky D, Calsyn DA, Shelton JL, Stolov WC, Rock DL. Pain measurement and pain behavior. **Pain** 1984; 18: 53–69.
41. Tedeschi JT, Schlenker BR, Bonoma TV. Cognitive dissonance: Private ratiocination or public spectacle? **Amer Psychol** 1971; 26: 685–695.
42. Ader R. Conditioned Immunopharmacological Effects in Animals: Implications for a Conditioning Model of Pharmacotherapy. In: White L, Tursky B, Schwartz GE, Eds. **Placebo—Theory, Research, and Mechanisms**. New York: Guilford Press; 1985.
43. Peck C, Coleman G. Implications of placebo theory for clinical research and practice in pain management. **Theor Med** 1991; 12: 247–270.
44. Voudouris NJ, Peck CL, Coleman G. The role of conditioning and verbal expectancy in the placebo response. **Pain** 1990; 43: 121–128.
45. Wall PD. Pain and the placebo response. **Ciba Found Symp** 1993; 174: 187–211.
46. Wickramasekera I. A conditioned response model of the placebo effect: Predictions from the model. In: White L, Tursky B, Schwartz GE, Eds. **Placebo—Theory, Research, and Mechanisms**. New York: Guilford Press; 1985.
47. Suchman AL, Ader R. Classic conditioning and placebo effects in crossover studies. **Clin Pharmacol Ther** 1992; 52(4): 372–377.
48. Iacono P, Drici MD, De Lunardo C, Salimbeni B, Lapalus P. Placebo effect in cardiovascular clinical pharmacology. **Int J Clin Pharmacol Res** 1992; XII(2): 53–56.
49. Mancia G, Omboni S, Parati G, Ravogli A, Villani A, Zanchetti A. Lack of placebo effect on ambulatory blood pressure. **Am J Health** 1995; 8: 311–315.
50. Weber MA, Neutel JM, Smith DHG. Controlling blood pressure throughout the day: Issues in testing a new anti-hypertensive agent. **J Hum Hypertens** 1995; 9(Suppl. 5): 29–35.
51. Report of Research Council Working Party on mild to moderate hypertension. Randomized controlled trial of treatment for mild hypertension: Design and pilot trial. **Br Med J** 1977; 1: 1437–1440.
52. Schindel L. Placebo und Placebo-Effekte in Klinik und Forschung. **Arzneimittelforschung** 1967; 17: 892–918.
53. Beecher HK. Die Placebowirkung als unspezifischer Wirkungsfaktor im Bereich der Krankheit und der Krankenbehandlung. In: Gross F, Beecher HK, Eds. **Placebo—das universelle Medikament? Paul-Martini-Stiftung der Medizinisch Pharmazeutischen Studiengesellschaft e.V.** Mainz: Eggebrecht-Presse; 1984.
54. Wolf S. The pharmacology of placebos. **Pharmacol Rev** 1959; 11: 689–704.
55. Hollister L. Placebology: Sense and nonsense. **Curr Ther Res** 1960; 2(9): 477–483.
56. Veterans Administration. Minutes of the Fifth Streptomycin Conference; Knickerbocker Hotel, Chicago, Illinois; April 15–18, 1948.
57. Green DM. Pre-existing conditions, placebo reactions, and "side effects." **Ann Intern Med** 1964; 60(2): 255–265.
58. Reidenberg MM, Lowenthal DT. Adverse nondrug reactions. **N Eng J Med** 1968; 279(13): 678–679.
59. Long DM, Uematsu S, Kouba RB. Placebo responses to medical device therapy for pain. **Stereotact Funct Neurosurg** 1989; 53: 149–156.
60. Ernst E, Resch KI. Concept of true and perceived placebo effects. **Br Med J** 1995; 311: 551–553.
61. Ho KH, Hashish I, Salmon P, Freeman R, Harvey W. Reduction of post-operative swelling by a placebo effect. **J Psychosom Res** 1988; 32(2): 197–205.
62. Hashish I, Harvey W, Harris M. Anti-inflammatory effects of ultrasound therapy: Evidence for a major placebo effect. **Br J Rheumatol** 1986; 25: 77–81.
63. Ross S, Krugman A, Lyerly S, Clyde D. Drugs and placebos: A model design. **Psychol Rep** 1962; 10: 382–392.
64. Marlatt A, Rohsenow D. Cognitive processes in alcohol use: Expectancy and the balanced placebo design. **Adv Subst Abuse** 1980; 1: 159–199.
65. Shapiro AK, Shapiro E. Patient-provider relationships and the placebo effect. In: Matarazzo JD, Weiss SM, Herd JA, Miller NE, Eds. **Behavioral Health: A Handbook of Health Enhancement and Disease Prevention**. New York: Wiley-Interscience; 1984: 371–383.
66. Peek CJ. A critical look at the theory of placebo. **Biofeedback Self-Regul** 1977; 2: 327–335.
67. Grünbaum A. Explications and implications of the placebo concept. In: White L, Tursky B, Schwartz GE, Eds. **Placebo—Theory, Research, and Mechanisms.** New York: Guilford Press; 1985.
68. Kirsch I, Weixel LJ. Double blind versus deceptive administration of a placebo. **Behav Neurosci** 1988; 102(2): 319–323.
69. Hornung J. Zur Problematik der Doppelblindstudien. **Therapeutikon** 1989; 3: 696–701.
70. Kirsch I, Rosadino MJ. Do double-blind studies with informed consent yield externally valid results? **Psychopharmacology** 1993; 110: 437–442.