



Placebo Therapy in Dermatology

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This article concerns the ambiguity of the placebo concept. It contains knowledge about the healing potential of the placebo effect with special attention to dermatology, and discusses the relationship between complementary and placebo therapy.

Background

Until the beginning of this century, the effects of most treatments were largely due to the placebo effect.¹⁻³ Nowadays, doctors only seldomly prescribe pure placebos.^{4,5} Still, even in modern, scientifically based medical and dermatological therapies, the therapeutic elements behind the placebo effect have a very important role to play.

There are only a few guidelines, however, about how to make the therapeutic elements of the placebo effect function. Their mechanisms are poorly understood, and very little is known about their healing potential. The main reason is the untreated control group is almost never included in trials. Only 12 trials with an untreated control group have been found in a search of the treatments of all diseases⁶ and only three trials on skin diseases.⁷⁻⁹ Thus, most reports of observed placebo effects are confounded by artefacts including spontaneous remission.⁶

A major reason for this methodologic error is that the word "placebo" is used with very different meanings. It has even recently been claimed that the placebo concept as presently used cannot be defined in a logically consistent way.¹⁰ Therefore, I am forced to start with the rather heavy task of thoroughly examining the placebo concept. This will also lay the groundwork for an understanding of the problems that arise when the placebo concept, despite its ambiguity, only too often is given a central role in discussions about complementary therapy.

Concepts

Earlier Definitions

For centuries "placebo" has meant a medicine adapted more to please than to benefit the patient.¹¹ After the first placebo-controlled trials were performed 50 years

ago, placebo came to mean an inactive therapy, used either as a control in trials, or as dummy therapy used in clinical practice for its psychologic effect.¹¹

How can a therapy, however, be called inactive, when it is shown to have a placebo effect? Shapiro answered this question by defining a placebo therapy not as inactive, but without specific effect.^{1,11,12} He defined placebo effect as the nonspecific psychologic or psychophysiologic effect of placebos, and implied that specific therapies may have placebo effects as well.¹

This definition of placebo has been preferred during the last 30 or so years,¹² but ambiguity remains: What do we mean by specific effect? What is the difference between a specific and a nonspecific effect, for example, in psychotherapy? Many alternative definitions have been suggested (e.g., "placebo effect" is synonymous with the effects of beliefs).¹³

Current Concept

There is still controversy about the exact definition, but the recommendation now is to understand the placebo effect as "... the effects observed in such a (parallel untreated control) group (subtracted) from those in the placebo group."⁶ This placebo concept has also been phrased as "... the difference in outcome between a placebo treated group and an untreated control group in an unbiased experiment," by an author who is well aware of its inborn difficulties.¹⁰

To estimate the magnitude of the placebo effect of a specific therapy, a trial with three groups is necessary: an intervention group, a placebo group, and an untreated control group. The effect observed in the untreated control group is subtracted from that in the placebo group, and the difference gives the placebo effect; however, a truly untreated control group does not exist, if one considers the effect of observation and diagnosis as a treatment.^{14,15} Untreated therefore here means that no overt (placebo) treatment is given after the diagnostic process.⁶

The following mechanisms are the ones possibly responsible for the healing rates observed in the untreated control group, and according to the current concept they do not contribute to the placebo effect:

- Spontaneous remission: The healing rates that would have been observed due to the natural history of the disease, even if no contact had been made with the health care system.

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- Effect of preliminary elements of the therapy: A phrase here used for the therapeutic elements of the clinical encounter that are active even before treatment is eventually offered. These elements consist of the meeting between therapist and patient, of history taking, investigations, diagnosis telling, and prognosis without treatment.
- Hawthorne effect: The extra effect of participating in a study.¹⁶
- Statistical regression toward the mean: The tendency of extreme measures to move closer to the mean when they are repeated.¹⁷

The effect of these mechanisms is thus subtracted from the effect observed in the placebo control group. The placebo effect is then solely the extra effect seen in the placebo-treated group, and it is attributable to the effect of what happens because the patient is receiving the placebo treatment and the circumstances under which this treatment is given.

Unfortunately, this placebo concept is not used by all authors, and most often the entire observed effect in the placebo treated control group, without subtraction of the healing rates of an untreated control group, is attributed to the placebo effect.^{6,18} This goes for dermatology as well.^{19,20}

Problems With the Current Concept

There are six problems with this conceptualization of placebo:

1. It makes sense only in relation to scientific trials and not in relation to practical therapy.
2. It only tells about the placebo effect and does not disclose what a placebo therapy is.
3. The possible healing effect of the diagnostic process and the other "preliminary elements of therapy" (see definition above) may be overlooked, because they will also be active in the "untreated" control group.
4. Trials with an untreated control group are very rare.⁶ The effect observed in the placebo treated control group is thereby confounded by the spontaneous remissions etc., and thus very little is known about the magnitude of the placebo effect itself,^{6,21} although there is no doubt about its clinical significance.²¹
5. In complex therapies, where many therapeutic elements interact, it may be hard to design a proper placebo therapy for trials. Whether or not the therapy is to be called a placebo depends upon the way the theory behind a therapy defines the therapy.
6. The "incidental elements of a therapy" (see definition below) risk being looked down on, since their effects are "just a placebo effect." Some (complementary) therapies contain incidental factors that may have a placebo effect substantially above the effect of ingesting a placebo tablet in which one believes.

Interpretation of Current Concept

It may seem like cryptic philosophy, but to understand the way the current placebo concept is problematic in relation to therapies that are more complex than pharmacologically active tablets, it is helpful to make a distinction between the defining and the incidental elements of a therapy¹² (in the article referred to the defining elements are called characteristic).

The defining elements of a therapy are the ones that define the therapy, and without which the therapy cannot be said to be of the specified kind; for example, the acetylsalicylic acid of a tablet against headache or the removal of the appendix in an operation for appendicitis.¹²

The incidental elements of a therapy accompany the defining elements, but they are not necessary for the therapy to be of the specified kind. They are what happens in conjunction with and after the therapy, and which would not have happened, had the therapy not been given. It could for example be the act of ingesting a tablet and the belief in its effect, or it could be the anesthesia and the incision in an operation for appendicitis.¹²

Using these terms in placebo-controlled trials, the intervention group will receive the defining as well as the incidental and the preliminary elements, whereas the placebo-treated control group will receive only the incidental and the preliminary elements. The untreated group receives the preliminary elements of the therapy.

Thus, the current concept of placebo effect being the difference in outcome between a placebo treated and an untreated control group is interpreted as follows:

- The placebo effect is the effect of the incidental elements of a therapy.¹²
- A placebo therapy is one that does not exert its effect through its defining elements.¹²

In placebo-controlled trials the defining factors will be deliberately removed from the treatment to design the placebo treatment. In clinical practice some therapies may also be placebos, simply because their defining elements are without any effect on the disease. In this way the first two of the above mentioned six problems of the current placebo concept are solved.

The third problem of the current placebo concept concerns the effect of the preliminary elements of a therapy that is not part of the placebo effect and may therefore be overlooked. The preliminary elements of a therapy are often more important than the incidental ones. Because their effects are often confused with the placebo effect, they will be discussed below together with the placebo effect. For clarification, the effect of a prognosis may be considered a preliminary as well as an incidental element. If the prognosis is given without any treatment, it is a preliminary element; however, if it

is given after a therapy, it represents an incidental element of the treatment.

Methodology: How Does the Placebo Effect Work?

The findings of trials on this subject differ considerably, indicating that it is individually and culturally determined what will create a placebo effect.^{13,22} When trials offer suggestions about achieving effect from a placebo treatment, it is seldom possible to determine whether the factor itself elicited the effect, or whether it actually enhanced the effect of the placebo.

Preliminary Elements of Therapy

A therapeutic effect after a placebo treatment is more likely when the patient regards the physician as experienced, competent and optimistic,^{22,23} and when the physician expects the treatment to help.^{24,25} The physician's attention may have a positive effect,²⁶ may comfort the patient, and may help by (unconsciously) demonstrating coping techniques in the way the physician responds to the patient's suffering.

Taking a thorough history may be therapeutic in itself.^{27,28} In many complementary therapies, the history taken is very long and may contain psychotherapeutic elements. During the history taking, the patient may change his thoughts about his illness and become aware of risk factors in his lifestyle.

If a patient is thoroughly examined, and many tests are performed, the patient may feel secure and become more likely to get well. The therapist's physical touch may relieve the anxiety of a patient who has feelings of guilt and ostracism, feelings that are not uncommon in the dermatologic patient.²⁹

Individualization

For maximum placebo effect the treatment should be individualized. For example, one experiment has clearly shown that mentally normal people respond with maximum placebo effect when the placebo is delivered with a neutral attitude from the therapist, whereas psychoneurotic and mentally rigid patients respond best to placebo treatments that are delivered with strong enthusiastic suggestions.³⁰

Two older trials have shown that several placebo tablets may have significantly more effect than one tablet.^{31,32} Not surprisingly, this effect is present only in patients who have a positive attitude toward taking tablets.³¹

Conditioned responses are often mentioned as a mechanism of action for the placebo effect.^{33–35} According to the conditioning theory, it would be generally advisable to offer a (placebo) therapy, whose incidental factors resemble a therapy which has formerly been experienced by the patient as effective. Some empirical

data support the hypothesis;³⁶ however, the body may not always react with a drug-mimicking conditioned reflex, but instead with a "drug anticipatory response," producing the opposite effects to the previously experienced ones.³⁷ For example, skin conduction^{38,39} and temperature³⁹ may be reduced as a drug anticipatory response to placebo beer, in some persons who have previously been exposed to alcohol in a similar fashion. Unfortunately, it is not clear under what circumstances a drug-mimicking conditioned reflex will occur, and when it will be a drug anticipatory response with the opposite effect.

Placebo Tablet: Mechanisms

The mechanisms behind the effect of something as simple as a tablet of calcium may be summarized as follows:

- Conditioning, as described above.
- To endure their symptoms some patients may need the tablet as a symbol of the therapist's support and may receive comfort from experiencing that something is being done.
- The patient's belief in a tablet may let him regain optimism and stimulate his species-preservative/trophotropic/pleasure system.²
- Biochemically and structurally, the following mechanisms have been suggested: endorphins,^{3,26,35,40–43} adrenocorticotrophic hormone^{40,44} melanocyte-stimulating hormone,⁴⁰ catecholamines,⁴⁰ gamma-aminobutyric acid,^{3,42} phenylethylamine,⁴⁵ descending serotonergic nerve fibers,⁴⁰ and noradrenergic neurons in the locus caeruleus in the brain stem.⁴⁰

Other Placebo Treatments

The color of a tablet may affect outcome.³²

Injections have been claimed to have more placebo effect than tablets.^{33,34} This is a dangerous myth, and the trial referred to³² does not support the hypothesis. On the contrary, a recent study has found that oral placebo had a significantly larger placebo effect than injections.⁴⁶

In four skin-related trials, gel or emollient seemed to have no placebo advantage over tablets,^{7–9,47} but in one trial it probably did.⁴⁸

With regard to complementary therapies, many other incidental factors may contribute to a strong placebo effect (e.g., belief, symbolism, meaning, shared world view, sympathy, physical touch, more time spent on the consultation, etc.).

Results: Healing Potential of Placebo Effect

A persistent myth claims that the placebo effect is almost constant and contributes with 33% of the effect of all therapies.³⁴ The myth stems from 1955⁴⁹ and is

clearly wrong, because the placebo effect is highly variable from trial to trial.^{6,34,42}

The fourth problem of the current placebo concept is the rarity of trials with an untreated control group. Practically all reports of placebo effects are invalidated by the effect of the factors that are also present in a no-treatment control group. This is one reason why the size of the placebo effect is still not determined and can only be estimated from suppositions. Another reason is that the factors responsible for the placebo effect are individual, fragile, and hard to grasp.

Placebo Tablet: Effects

Does a simple placebo treatment such as a tablet of calcium produce a placebo effect? On a group basis, the answer seems to be “no,” unless extra preliminary and incidental factors are added together with the placebo.

In the three studies on skin diseases with a no-treatment control group, there was no difference at all in outcome between the placebo treated and the untreated control group.^{7–9}

This confirms the general finding that patients who are told that no treatment is needed fare exactly as well as those who receive a placebo treatment.^{50,51} Other trials have reached the opposite conclusion^{52,53} but their methodology makes them less convincing. Others have found a very small placebo effect.⁵⁴ It may, however, be different for treatments in daily practice, where belief may be stronger. If the placebo tablet is followed by extra attention from the therapist, an extra effect may be expected.

Type of Patient

Anxious and tired patients obtain the greatest placebo effect,⁵⁵ just as those do who are highly motivated to get well.⁵⁶ Improvement also seems to be more likely to occur when the patient is expecting something to happen,⁵⁷ and if the patient has a desire for the kind of treatment, which is given.⁵⁵ Suggestible patients probably do not exhibit a greater placebo than other patients.^{42,58,59} Intelligence and sex do not seem to matter.^{3,42,60}

Diseases Influenced by Placebo Effect

Illness behavior⁵⁰ and pain^{6,22,61} are influenced by placebo, with depression and neurotic symptoms also being susceptible to influence.^{31,55} There are even significant but questionable effects on inflammatory swelling,^{61,62} blood pressure,³⁶ and C-reactive protein.^{61,62}

Dermatologic Diseases

In the three trials on skin diseases in which a no-treatment control group was included, no extra effect was seen in the placebo-treated control group [the investigated treatments were: (1) aloe vera gel vs. placebo

gel vs. no treatment against radiation-induced skin toxicity;⁷ (2) antiperspirant emollient vs. placebo vehicle vs. no treatment against blister formation on the feet;⁸ and (3) hypnotic vs. salicylic acid vs. topical placebo compound vs. no treatment against warts.⁹]

The physical state of several dermatologic diseases is thought to be influenced by different kinds of psychotherapy,^{29,63} although emotional factors play a primary and pathogenic role in only a few instances,²⁹ and although research has often lacked control groups, follow up, and sufficient numbers of patients.⁶³ It seems plausible that the diseases thought to be influenced by psychotherapy may also be influenced by the preliminary and incidental elements of more tangible (complementary) therapies, because some of the same mechanisms may be at work (emotional support and a safe structure, in which the patient can explore feelings and actions),⁶³ and because they may inspire hope and a feeling of control, and may relieve stress. Empirical data support the hypothesis of some resemblance between placebo and psychotherapy.⁶⁴

The skin disorders that may be influenced by the preliminary and incidental factors of therapies will be briefly mentioned and classified in the following five groups. The diseases are categorized on the basis of the available literature which may not always be substantive.

- Skin disorders, that may in some patients be influenced by psychological intervention: Pruritus,²⁹ chronic urticaria,^{63,65,66} psychogenic purpura syndromes,⁶³ alopecia areata,^{63,65} psoriasis,^{29,63,65,67} atopic dermatitis,^{29,63,65,68} warts,^{9,65} hypersensitivity,^{69–71} and perhaps Raynaud’s disease.^{72,73} In general, pain responds to placebo,^{6,22,61} and pain-prone skin disorders probably do as well.
- Skin disorders, for which emotional factors are precipitating or perpetuating: Lichen planus,⁶⁵ dyshidrosis,²⁹ seborrheic dermatitis,^{29,74} aphthosis,²⁹ herpes simplex,⁷⁴ and rosacea.^{29,74}
- Skin disorders that are primarily psychiatric or emotional in origin: Delusions concerning the skin,^{29,74} the factitial syndromes,^{29,65,74} and neurotic excoriations, trichotillomanias and other compulsive habits.^{29,63,65,74} These are often better cared for by a psychiatrist, but not seldom the patient will resist referral.⁷⁴ Often these diseases are beyond the reach of superficial psychotherapy;^{29,74} however, in some patients there may be an effect,^{29,63,65,74} where the preliminary and incidental factors of other therapies should not be precluded.
- Skin disorders that are influenced by behavior: Other dermatologic problems, for which the patient’s behavior plays a pathogenic role include infections (poor hygiene) and toxic dermatoses (carelessness),

may also be influenced by the preliminary and incidental elements of therapy.

- The psychological distress of skin diseases: In a vulnerable subject any skin disease may cause severe psychological problems.⁷⁴ Direct psychotherapy or psychotropic drugs will usually be the treatment of choice in these cases, but it should be remembered that such patients may also benefit psychologically from the preliminary and incidental elements of other treatments as well, even if the defining elements of the therapy have no effect on the disease.

Side effects

Adverse reactions may occur after placebo treatment,^{3,25,34,40,55,75} and this has been observed in dermatology, as well.^{76,77}

Discussion: Complementary Medicine and Use of Placebo

Is Complementary Therapy Placebo?

The fifth problem of the current placebo concept is that it may be hard to design placebo treatments for complex therapies, because it may be hard to decide on the defining elements of the therapy. It depends how an actually performed therapy is defined by its underlying theory, whether it is a placebo or not.

Say, as a hypothetical example, that it was known that acupuncture, 1 hour twice weekly, had a beneficial effect on psoriasis. What transpires if it was the relaxation that worked and that it did not matter where the needle was inserted. If then acupuncture for psoriasis is defined as the insertion of a needle at a specific spot, the treatment will be a pure placebo, because its only mechanism of action is through the incidental element of relaxation. If the relaxation is considered a central part of the therapy, acupuncture for psoriasis should no longer be termed a placebo, because one of its defining elements is responsible for its effect.¹²

If a therapy is imprecisely defined, it will remain debatable, whether the therapy is a placebo or if it deserves to be called a specific therapy. In placebo-controlled trials of complex therapies some of the therapeutic factors will often be present in the placebo treatment as well as in the specific therapy, and their effect considered "just a placebo effect." If the defining elements are without effect, the treatment is in danger of being underestimated, because its incidental elements are overlooked.

The placebo concept is grounded in a pharmacologic worldview and seems to be less relevant in relation to complementary and other complex therapies.

The problem may be solved by not asking whether a therapy is a placebo.¹⁰ Instead, the two important questions are: Does the therapy work? and, if it does: What part of the therapy is responsible for its action?

To answer the first question, a no-treatment control group is necessary.^{6,10} The problem is that it is then not possible to blind the patient, and part of the treatment effect may stem from something as fragile as expectations.

To answer the second question, component control trials instead of placebo controlled trials may be a solution.⁷⁸

This does not solve all the problems of complementary therapy research. Complementary therapies may be fragile to experimental circumstances, and therefore epidemiologic research methods are necessary, as well. Complementary therapies may have effects that are only detectable by qualitative research methods.

In daily clinical practice, the placebo concept is probably of limited value, as well.¹⁰ From the first contact with the patient, the clinician will seek that everything done helps to improve the patient's health, and a sharp distinction between diagnostic process and treatment cannot always be made.²⁸ This is especially evident in relation to family practice and psychiatry but goes for most medical work, including dermatology.

If attention is not paid to whether a therapy should be called a placebo, the sixth problem of the current placebo concept is solved, namely that it includes all the incidental elements of a therapy and that these elements therefore risk being looked down on. If the placebo concept remains in focus, the relativity of the concept should be remembered, and the healing potential of its underlying elements should be respected.

Using the Placebo Effect

Preliminary Elements

All physicians should be aware of the therapeutic potential of the preliminary elements of therapy and use it for the benefit of his patients. In dermatology, however, the therapeutic effect of the physician's personality²⁹ and the relation with the patient⁶³ is often underrated, perhaps because contacts are often brief.⁶³

Incidental Elements

The incidental factors of a therapy should be considered, especially if the placebo consists of something more complex than an orally taken agent. For example, a simple treatment such as a cream or an ointment has the incidental factors of touch and attention, which might diminish unconscious scratching.

In complementary therapies, the incidental elements may be far more complicated, and the physician should consider these before he rejects a therapy whose defining elements are unlikely to have an effect.

Using a Placebo Treatment

Even though a placebo tablet on a group basis is not better than reassurance alone, many therapists have occasionally used it,^{4,5,79} explaining that the patient needs a focus for improvement, or demands a treat-

ment.⁵ Generally such practice undermines confidence and should be abandoned, except perhaps when the patient's belief is very strong. In these few instances, the patient may experience a placebo effect.

Often, family practitioners will not offer a pure placebo.⁵ If they judge that a patient needs a placebo, some will instead offer a treatment with only weak pharmacological content.⁵ In this way, too many unnecessary treatments will be used until it is generally realized that the preliminary factors may well be put in action without any treatment.⁵⁰ The preliminary factors should not be confused with the effect of giving a placebo treatment.

Conclusions

Those elements of a therapy that are not defining for the therapy in question may be conceptually split into the preliminary and incidental elements of the therapy. These elements often have important healing potentials.

The current concept of the placebo effect may be interpreted as the effect of the incidental elements of therapy. The preliminary and incidental elements of therapy should not be overlooked in the evaluation of complementary and other complex therapies, nor in daily clinical practice.

The way is individual, by which the physician achieves a therapeutic effect from the preliminary and incidental elements of a therapy, but an empathic, optimistic, and competent attitude on the part of the caregiver seems to have the greatest effect. The preliminary and incidental elements may have the biggest therapeutic potential in the frightened patient, but only very seldom is any extra effect achieved by prescribing a pharmacologically inactive product if its incidental elements are not profound.

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