Psoriasis: Targets and Therapy

Dovepress
Taylor & Francis Group

Open Access Full Text Article

CLINICAL TRIAL REPORT

# Shaping Treatment Expectation to Optimize Efficacy of Interleukin 17A Antagonist Secukinumab in Psoriasis Patients

Stefanie Hölsken[1], Frederik Krefting[2], Senta Mühlhaus[2], Daniela Bese[2], Manfred Schedlowski[1,3], Wiebke Sondermann[2]

[1]Institute of Medical Psychology and Behavioral Immunobiology, University Hospital Essen, University of Duisburg-Essen, Essen, Germany; [2]Department of Dermatology, Venereology and Allergology, University Hospital Essen, University of Duisburg-Essen, Essen, Germany; [3]Department of Clinical Neuroscience, Osher Center for Integrative Medicine, Karolinska Institutet, Stockholm, 171 77, Sweden

Correspondence: Stefanie Hölsken, Institute of Medical Psychology and Behavioral Immunobiology, University Hospital Essen, Hufelandstraße 55, Essen, 45147, Germany, Email Stefanie.Hoelsken@uk-essen.de



**Purpose:** Patients' treatment expectations significantly influence the effectiveness of medical and pharmacological treatments. This clinical proof-of-concept study aimed to enhance treatment outcomes by targeting positive treatment expectations of psoriasis patients beginning systemic anti-psoriatic therapy with secukinumab, an interleukin (IL)-17A antagonist.

**Patients and Methods:** We randomly assigned patients to three groups: a treatment as usual (TAU) group receiving the standard 300mg dose of secukinumab, a dose-control (DC) group with 75% dose reduction and an experimental (EXP) group receiving the same reduced dose along with a "cover story" designed to positively influence treatment expectations. We evaluated skin symptoms using the Psoriasis Area and Severity Index (PASI), the Dermatology Life Quality Index (DLQI), perceived itch, mood and plasma IL-17A levels at baseline and at 1, 2, 3, 4, 8, 12, and 16 weeks post intervention.

**Results:** The study included N = 120 patients (average age = 45.78 years, 34% female). A high baseline expectation level (8.1 of 10 points) was observed across all groups which could not be further increased by the EXP-group's "cover story". The EXP and DC groups did not differ with regard to reaching 75% improvement in PASI scores (PASI75), a DLQI score of 0 or 1 or at least 4 points improvement in itch. Over time, the EXP-group showed a faster decline in PASI scores and anxiety symptoms compared to the DC-group, but less improvement in quality of life. IL-17A levels significantly increased throughout the treatment, with no significant differences between groups despite the 75% dose reduction.

**Conclusion:** This study demonstrates an attempt to modify patients' treatment expectations to enhance the effectiveness of pharmacological therapy with secukinumab in psoriasis patients. However, verbal suggestion alone did not significantly improve clinical outcomes, suggesting that future studies should explore alternative approaches to leverage placebo effects to the benefit of patients with psoriasis.

**Keywords:** psoriasis treatment, psychodermatology, placebo effect

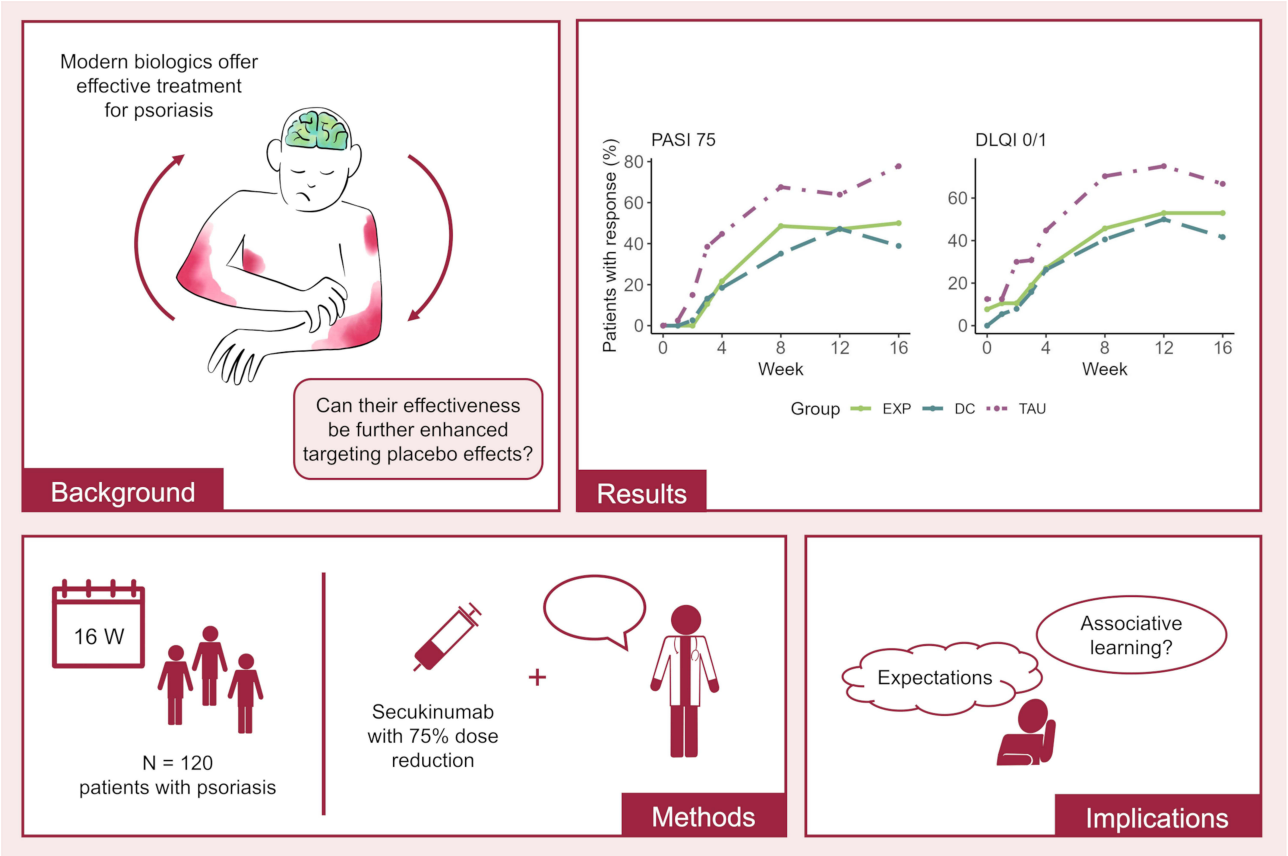
## Introduction

Drugs do not operate in isolation. When a doctor prescribes a pill, its effectiveness is shaped not only by its chemical interaction with the body, but also by the patient's psychological and biological condition. This condition is affected by various elements including genetic makeup, emotional and motivational states like the patient's expectations of the drug's outcomes, and prior experiences with this treatment or treatments in general.[1] Together, these components can enhance the overall effectiveness of the treatment, a phenomenon known as *placebo effect*.[2,3]

Placebo effects modulate symptom perception, disease courses, and the efficacy and tolerability of medical treatments.[4] They are based on complex neurobiological phenomena involving the contribution of central as well as peripheral physiological mechanisms.[5,6] Solid experimental and clinical data demonstrate convincing placebo effects in

Received: 10 July 2024
Accepted: 26 November 2024
Published: 10 January 2025

**Graphical Abstract**




particular in pain and affective diseases.[4,7,8] Large placebo responses in clinical trials of chronic inflammatory skin diseases such as atopic dermatitis or psoriasis suggest that the mechanisms detailed above should also be considered in the therapeutic context of dermatological diseases.[9,10]

This view is supported by experimental evidence in healthy subjects, allergic patients and those with atopic dermatitis.[11–13] The studies demonstrate that both subjective symptoms such as itch and objective markers such as wheal size or basophil activation can be reduced by employing verbally manipulated expectations and learning experiences in the form of classical conditioning. Preliminary outcomes furthermore suggest that harnessing placebo effects may be a viable option to enhance treatment outcome in patients suffering from chronic inflammatory diseases.[13,14]

To assess the generalizability of findings from pain and affective research, studies in dermatological patient cohorts are needed. One that may provide a good model is that of persons suffering from psoriasis, as the brain-skin axis was shown to play an important role in this disease.[15,16] Psoriasis is a chronic inflammatory skin disease, characterized by scaly, erythematous plaques that can cover large portions of the body and often cause intense itch.[17] With about 2–3% of the population in western societies affected, it is a comparatively common disease.[18,19] Based on an improved understanding of the underlying pathophysiology,[20] recent years have seen radical improvement in the availability and effectiveness of medications.[21] However, these modern biologic treatments are costly[22] and therefore mostly not prescribed as a first-line treatment.[23,24] Harnessing placebo effects to improve treatment outcomes therefore might be a viable option to reduce the dosages needed, thereby lowering costs for the healthcare system and making highly effective treatments available to more patients.

 https://doi.org/10.2147/PTT.S486338 

Thus, we employed a dose-reduction regimen of an effective systemic treatment for psoriasis with the interleukin (IL)-17A antagonist secukinumab in combination with the intake of a novel tasting drink accompanied by a cover story to shape patients' expectations. We compared this group with a dose-control group and assessed both subjective (quality of life, itch, and pain) as well as objective (dermatologist-rated skin symptoms) outcomes.

# Materials and Methods

## Design

The protocol of this study was published[25] and registered online (https://drks.de/search/de/trial/DRKS00022104). The study received approval from the institutional ethics committee of the University-Duisburg Essen (IRB protocol number 19–8636-BO) and complies with the Declaration of Helsinki. It was conducted as part of a collaborative research center on treatment expectations.[26] Reporting followed the CONSORT criteria for randomized trials (see CONSORT checklist in supplementary Table 1).[27]

Figure 1 illustrates the study design. Patients were randomly assigned to three groups in equal ratios. The standard dose group (treatment as usual, TAU) received 300mg of the IL-17A inhibitor secukinumab.[28] The dose-control group (DC) received 75mg secukinumab (75% reduction), as did the experimental group (EXP), which in addition received a novel tasting drink and suggestions of heightened treatment expectations. Over 16 weeks, patients followed the secukinumab administration protocol, with assessments of both objective and subjective outcomes at each visit. Pain was rarely reported and therefore excluded from analyses.

## Participants and Recruitment

Patients were eligible for participation if they had a Psoriasis Area and Severity Index (PASI)[29,30] of at least 12 and a Body Surface Area (BSA)[31] affected by plaque psoriasis of at least 10%. Additional inclusion criteria were derived from the summary of product characteristics for secukinumab.[28] Patients were primarily recruited through the outpatient department of the Department of Dermatology, Venereology and Allergology, University Hospital Essen. In addition, advertisements were sent to dermatologists and posted on social media.

## Procedure

All study visits were conducted at the Department of Dermatology, Venereology and Allergology, University Hospital Essen. Data collection lasted from October 2020 until November 2023 and ended with the final patient's last scheduled visit.

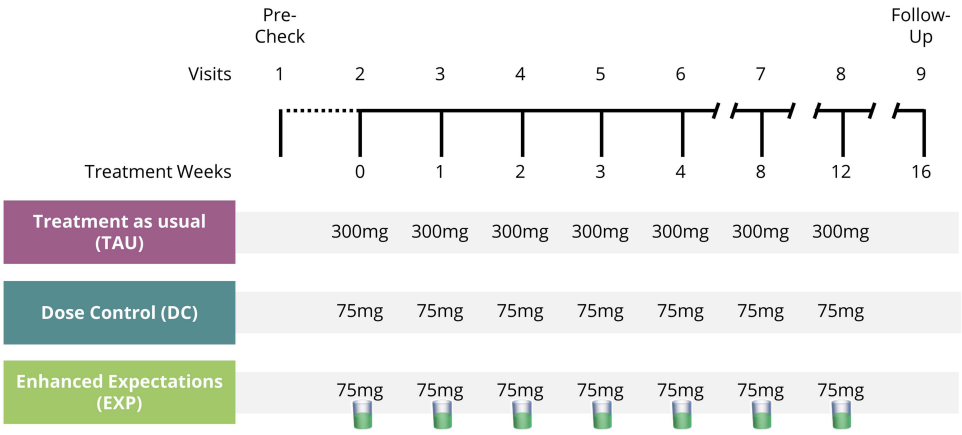



**Figure 1** Study Design. After an initial pre-check, patients were randomly allocated to one of three treatment groups: The treatment as usual (TAU) group received the full dose of secukinumab as in clinical routine (300mg) and served as pharmacological control. The dose reduction control group (DC) was administered only 75mg of secukinumab (75% reduction) during all treatment weeks. Patients in the enhanced expectation group (EXP) were treated with the same dose reduction regimen as the DC group but received an additional verbal instruction together with the ingestion of a novel tasting beverage to increase the salience of this verbal suggestion. At follow-up, all outcome parameters were measured again and continuation of treatment outside of the study was discussed with patients.


https://doi.org/10.2147/PTT.S486338

During the initial visit, a responsible physician conducted a screening examination to confirm the diagnosis of plaque psoriasis and patients' eligibility for systemic treatment with secukinumab. Patients were thoroughly informed about the study procedures and the potential risks associated with the treatment. This session also provided an opportunity for patients to ask questions prior to providing their written informed consent. Patients were then randomized to one of three groups using computer-generated random numbers. Participants' data were pseudonymized using the software ALIIAS (Anonymization with LimeSurvey Integration and II-Factor Authentication for Scientific Research, version 0.9).[32]

At each study visit, the participants were welcomed by the study team and escorted to a private treatment room where they completed various questionnaires (details in the *Measures* section). A dermatologist who was blinded with regard to group allocation then assessed the patients' skin symptoms. The study physician checked on the patients for any new concerns. With the exception of screening and follow-up visits, patients then received their prescribed medication. To maintain blinding with respect to the dosage, patients were blindfolded while receiving subcutaneous injections. Additionally, patients in the EXP group were given a novel tasting gustatory stimulus (100mL of green-colored strawberry milk with 5 drops of lavender oil; for references, see[11,33]) just before the injection. This drink was described by the physician as an additional treatment enhancer purported to activate the "body's own pharmacy", a concept introduced to the patients during the initial administration (for the script see supplementary Table 2) and briefly reminded at subsequent visits. The unusual taste was intended to increase the salience of the stimulus. Blood samples were collected every four weeks before drug administration for clinical routine assessments and IL-17A analysis.

The follow-up visit occurred 16 weeks after the initiation of treatment, when all outcome parameters were re-assessed. At this visit, patients were un-blinded, and the possibility of continuing treatment with secukinumab under usual care conditions was discussed.

## Measures

Patients' skin symptoms were assessed using the PASI. To evaluate subjective symptoms, patients completed the Dermatology Life Quality Index (DLQI)[34] and rated their current experience of itch and pain on a 100-point visual analogue scale (0.0–10.0 VAS). Additionally, they reported their current symptoms of depression and anxiety on the State-Anxiety-and-Depression-Scale (STADI).[35]

Patients' clinically meaningful outcomes were included in secondary analyses; these comprised a 75% reduction in PASI score (PASI75),[36] a DLQI score of zero or one (DLQI 0/1) and a reduction on the pruritus visual analogue scale of at least four points (P-VAS ≥4-point improvement).

At the screening visit and again one week after the first administration of medication, patients rated their treatment expectations in the Generic rating scale for previous treatment experiences, treatment expectations, and treatment effects (GEEE).[37]

To validate the effect of the experimental manipulation on the patients' immune system, IL-17A was measured in the patients' blood plasma. To this end, blood samples were drawn into tubes containing an anti-coagulant (S Monovette EDTA, Sarstedt, Nümbrecht, Germany) and separated using centrifugation (2000g, 10 min, 4°C). Plasma samples were stored until analyses at −80°C. Analyses were performed using a Meso Scale Discovery assay (MSD, Rockville, Maryland, USA; detection limit: 1.03–9.46 pg/mL).

## Statistical Analyses

The sample size of N = 120 was determined a priori employing G*Power (Version 3.1.9.2,[38] for details see[25]) and taking into account an anticipated drop-out rate of 20%. Data was curated with IBM SPSS Statistics (Statistical Package for Social Science, SPSS Inc., Chicago, version 27) and analyzed using base R (version 4),[39] and the R-package nlme.[40] Plots were created using ggplot2.[41] Up to one missing datapoint per patient was imputed using linear regression and median insertion.

Potential differences in baseline demographics were assessed using Chi²-test for dichotomous, or analysis of variance (ANOVA) for continuous variables. For each continuous dependent variable, a mixed linear model was built using group (3 levels) and study visit (8 points in time) as independent variables. Clinically meaningful outcomes were analyzed calculating each patient's area under the curve (AUC with respect to ground)[42] and comparing the groups in one-way

ANOVAs and post-hoc pairwise *t*-tests. Group differences in the GEEE score of positive treatment expectations were analyzed using the Kruskall Wallis test, with False-Discovery Rate (FDR)-corrected post-hoc Dunn tests.

# Results

## Sample

A total of N = 120 patients were initially included in the study as illustrated in the CONSORT flow diagram (Figure 2). Of these, 34.17% were female. The sample's mean age was 45.7 years, ranging from 20.6 to 83.7 years. 12.5% of patients suffered from comorbid psoriatic arthritis (refer to supplementary Table 3 for additional comorbidities). On average, patients had received 13.7 years of formal education (range 3.5–35 years). While these three parameters did not significantly differ between groups, both the body mass index (BMI) and baseline PASI score were significantly higher in the EXP group (BMI: $F = 3.12$, $p = 0.048$; PASI: $F = 3.42$, $p = 0.036$). Spearman's rank correlation test indicated a significant correlation between baseline PASI and BMI ($rho = 0.20$, $p = 0.030$). There were no significant differences between the groups regarding baseline levels of the other two outcome measures DLQI and itch, nor in anxiety and depressive symptoms (Table 1).

## Expectations

Figure 3 depicts positive treatment expectations at the screening visit and after one week of treatment. Groups did not differ significantly in their expectations at baseline ($\chi^2 = 3.60$, $p = 0.165$) and showed no significant differences regarding

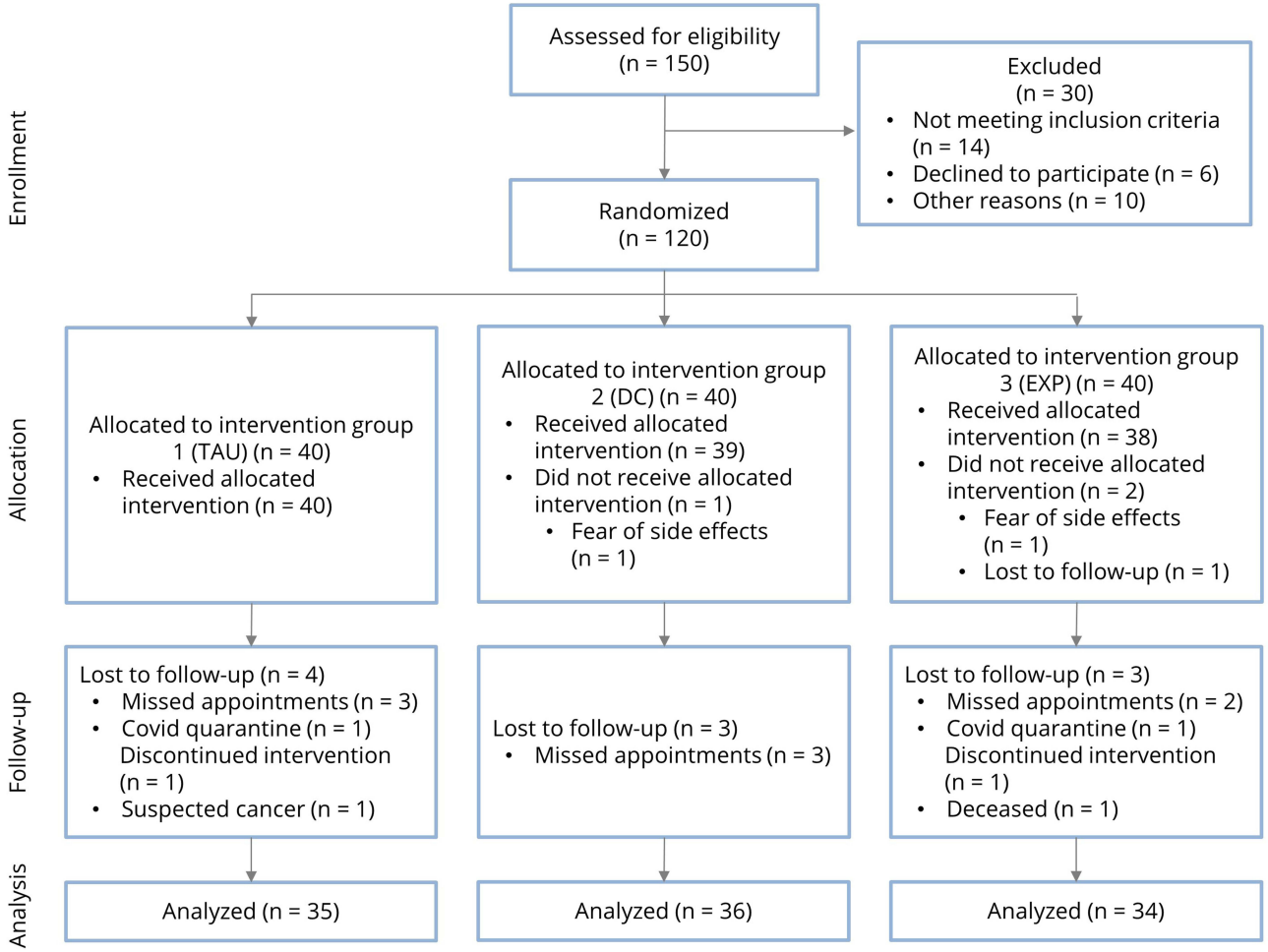



**Figure 2** CONSORT Flow diagram.

**Abbreviations**: TAU, Treatment as usual group with 300mg of secukinumab application; DC, Dose control group with 75mg secukinumab application; EXP, enhanced expectation group with 75mg secukinumab application + verbal suggestion to heighten expectations.


https://doi.org/10.2147/PTT.S486338

**Table 1** Baseline Demographics

| | Total | TAU | DC | EXP | Test |
|---|---|---|---|---|---|
| % Female | 34.17 | 35.00 | 40.00 | 27.50 | $\chi^2$ = 1.41<br>p = 0.495 |
| Age (years) | 45.78<br>(20.66–83.79) | 47.54<br>(20.66–73.28) | 47.16<br>(22.32–74.36) | 42.66<br>(20.89–83.79) | F = 1.30<br>p = 0.275 |
| BMI | 30.17<br>(18.21–52.94) | 29.7<br>(18.65–51.32) | 28.1<br>(18.21–50.70) | 32.7<br>(19.53–52.94) | F = 3.12<br>p = 0.048 |
| Education (years) | 13.77<br>(3.5–35) | 14.12<br>(8–26) | 14.56<br>(3.5–35) | 12.65<br>(5–22) | F = 2.07<br>p = 0.131 |
| Baseline PASI | 14.22<br>(2.7–31.60) | 13.06<br>(2.7–31.6) | 13.18<br>(3.7–27.1) | 16.45<br>(3.7–28.8) | F = 3.42<br>p = 0.036 |
| Baseline DLQI | 10.60<br>(0–27) | 10.23<br>(0–26) | 11.15<br>(2–27) | 10.44<br>(0–24) | F = 0.22<br>p = 0.807 |
| Baseline Itch | 5.38<br>(0–10) | 5.10<br>(0–10) | 5.45<br>(0.8–10) | 5.61<br>(0–10) | F = 0.32<br>p = 0.727 |
| Baseline Pain | 2.86<br>(0–10) | 2.41<br>(0–8.5) | 3.24<br>(0–10) | 2.93<br>(0–10) | F = 0.93<br>p = 0.399 |
| Baseline Depression (STADI) | 20.85<br>(10–37) | 20.98<br>(13–32) | 21.55<br>(14–37) | 20.03<br>(10–33) | F = 0.91<br>p = 0.406 |
| Baseline Anxiety (STADI) | 19.11<br>(11–34) | 19.68<br>(11–34) | 19.28<br>(11–27) | 18.38<br>(12–30) | F = 0.75<br>p = 0.473 |

**Notes**: Continuous variables are given as mean values with the range in parentheses. Itch and pain were rated by the patients on a 0.0–10.0 visual analogue scale. Chi² test was used to analyze differences in the proportion of female patients, analysis of variance (ANOVA) for all other outcome variables.

**Abbreviations**: TAU, Treatment as usual group with 300mg of secukinumab application; DC, Dose control group with 75mg secukinumab application; EXP, enhanced expectation group with 75mg secukinumab application + verbal suggestion to heighten expectations; PASI, Psoriasis Area and Severity Index; DLQI, Dermatology Life Quality Index; STADI, State-Trait Anxiety and Depression Inventory.

changes in expectations between assessments ($\chi^2$ = 0.61, p = 0.736). This indicates that the verbal suggestion, which occurred between assessments, did not have a significant influence on overt expectations. Notably, the initial mean expectation rating was 8.1 out of 10 points across groups, indicating a potential ceiling effect in this measure.

## Primary Outcomes

Absolute numbers for each of the three primary outcomes over the course of treatment are presented in Figure 4. The analysis of PASI scores identified outliers that significantly influenced the results. Six data points that lay more than three standard deviations from the sample means were therefore excluded from the analysis. Across groups, there was a significant improvement of all assessed symptoms over the time of treatment, expressed in a significant main effect of time (PASI: F = 588.53, p < 0.001; Itch: F = 440.78, p < 0.001; DLQI: F = 524.29, p < 0.001).

The comparison of treatment groups revealed significantly higher PASI scores in the EXP group (main effect of group: F = 11.78, p < 0.001). At the same time, the EXP group showed a steeper decline in PASI scores over time compared to the DC group, with a mean improvement of 11.01 points compared to 9.02 points (time x group interaction effect; F = 4.73, p = 0.009). Detailed group comparisons can be found in Table 2. 78% of patients in the TAU group achieved a PASI75 response at week 16, compared to 50% in the EXP and 39% in the DC group. Statistical analysis of the AUC revealed a significant advantage of the TAU group, while there was no significant difference between the two dose-reduced groups (for details see Table 3).

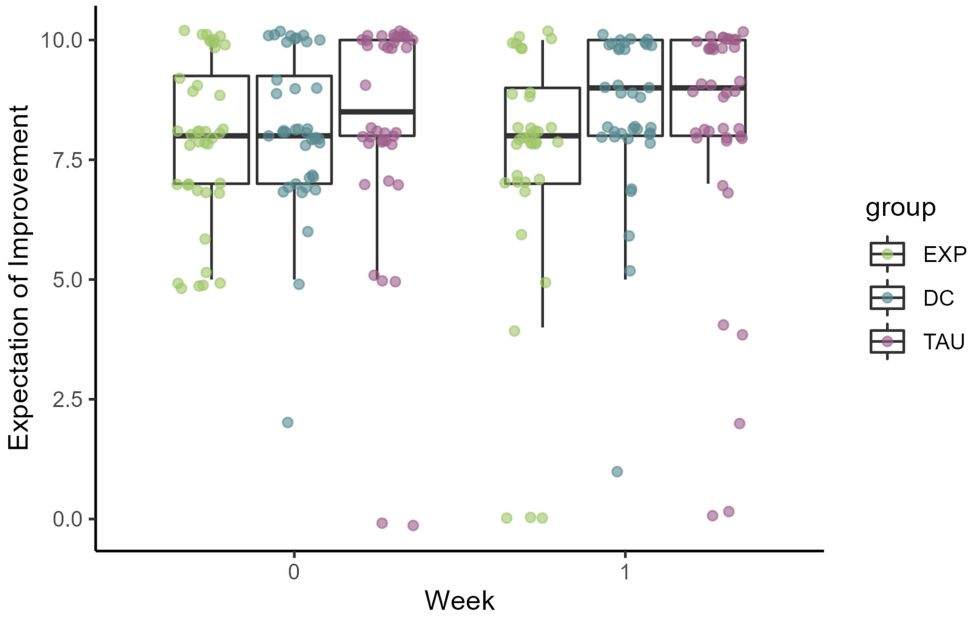



**Figure 3** Expectation ratings. Positive treatment expectations, assessed with the GEEE scale on a 0–10 numeric rating scale. Ratings were collected prior to (week 0) and after (week 1) the experimental intervention, involving the verbal suggestion of probable treatment success supported by a novel tasting drink for the experimental (EXP) group.
**Abbreviations**: DC, Dose control group; TAU, Treatment-as-usual group.

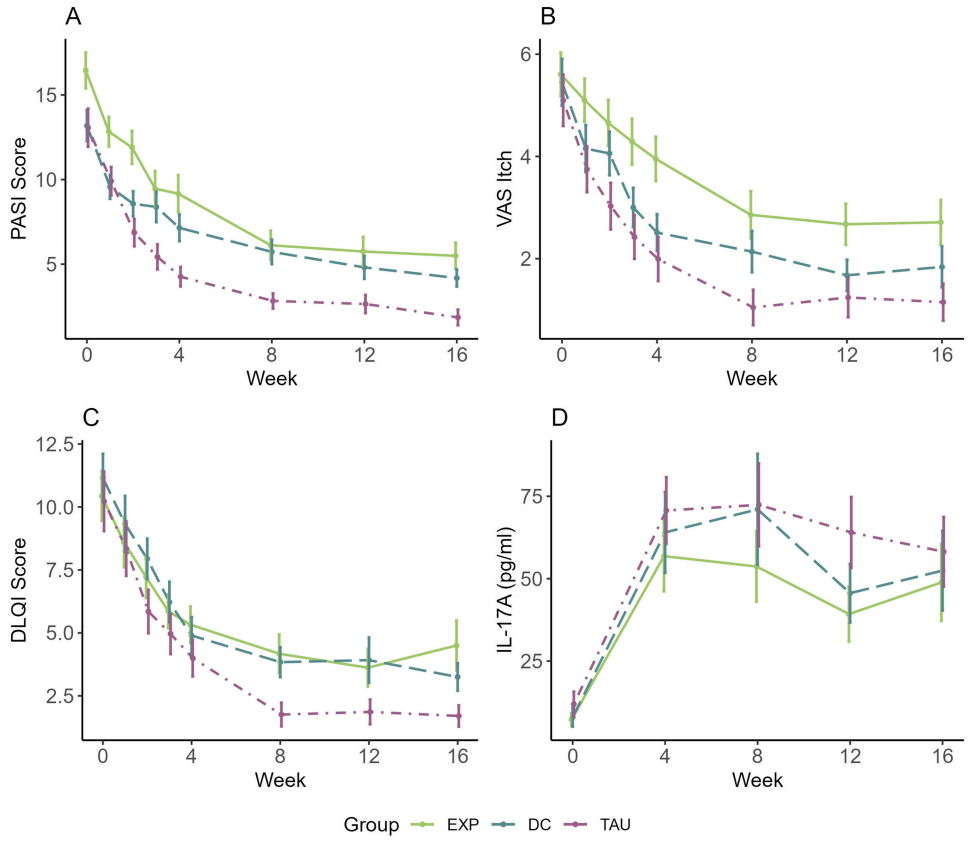



**Figure 4** Absolute numbers over the course of treatment for the three primary outcomes. (**A**) Psoriasis Area and Severity Index (PASI) over the course of treatment; (**B**) Itch ratings on a visual analogue scale (VAS) ranging from 0–10; (**C**) Dermatology Life Quality Index (DLQI), with higher numbers indicating higher burden on quality of life; (**D**) Interleukin (IL)-17A measured in the blood plasma.
**Abbreviations**: TAU, Treatment as usual group with 300mg secukinumab application; DC, Dose control group with 75mg secukinumab application; EXP, enhanced expectation group with 75mg secukinumab application + verbal suggestion to heighten expectations.


https://doi.org/10.2147/PTT.S486338

**Table 2** Mixed Model Results of Primary Outcomes

| Dependent Variable | Group | N | Effect | Test Statistic | Significance | Likelihood Ratio |
|---|---|---|---|---|---|---|
| PASI | TAU | 40 | Intercept | F = 605.32 | p < 0.001 | |
| | DC | 39 | Time (main effect) | F = 588.53 | p < 0.001 | 431.75 |
| | EXP | 39 | Group (main effect)<br>a. EXP vs DC<br>a. EXP vs TAU | F = 11.78<br>t = −3.54<br>t = −3.53 | p < 0.001<br>p = 0.001<br>p = 0.001 | 24.17 |
| | | | Time*Group (interaction)<br>a. Time*EXP vs DC<br>a. Time*EXP vs TAU | F = 4.74<br>t = 2.68<br>t = 0.08 | p = 0.009<br>p = 0.007<br>p = 0.936 | 5.07 |
| Itch | TAU | 40 | Intercept | F = 285.24 | p < 0.001 | |
| | DC | 39 | Time (main effect) | F = 440.78 | p < 0.001 | 344.36 |
| | EXP | 39 | Group (main effect)<br>a. EXP vs DC<br>a. EXP vs TAU | F = 5.30<br>t = −0.91<br>t = −1.71 | p = 0.006<br>p = 0.364<br>p = 0.089 | 10.74 |
| | | | Time*Group (interaction)<br>a. Time*EXP vs DC<br>a. Time*EXP vs TAU | F = 1.57<br>t = −0.83<br>t = −1.77 | p = 0.209<br>p = 0.409<br>p = 0.078 | 4.74 |
| DLQI | TAU | 40 | Intercept | F = 241.66 | p < 0.001 | |
| | DC | 39 | Time (main effect) | F = 524.29 | p < 0.001 | 394.69 |
| | EXP | 39 | Group (main effect)<br>a. EXP vs DC<br>a. EXP vs TAU | F = 1.53<br>t = 1.44<br>t = 0.53 | p = 0.221<br>p = 0.153<br>p = 0.594 | 6.25 |
| | | | Time*Group (interaction)<br>a. Time*EXP vs DC<br>a. Time*EXP vs TAU | F = 6.38<br>t = −2.77<br>t = −3.35 | p = 0.002<br>p = 0.006<br>p = 0.001 | 7.45 |

**Notes**: Likelihood ratio = likelihood of the data comparing a model including a given effect to a model including only the mean of the outcome variable, thereby illustrating the added benefit provided by each variable as a measure of effect size. For the analysis of PASI scores, six data points that lay > 3 standard deviations from the sample mean were excluded. The outlier data points stemmed from five different patients, of whom four were in the EXP group and one was in the DC group. These five patients were older than the general cohort (52.98 vs 45.78 years), had a higher BMI (40.74 vs 30.17) and only one of the five was female (20% vs 34.17%). * denotes a multiplication, ie separates the factors underlying the interaction effect.
**Abbreviations**: PASI, Psoriasis Area and Severity Index; DLQI, Dermatology Life Quality Index; N, number of patients analyzed; TAU, Treatment as usual with 300mg secukinumab; DC, Dose control with 75mg secukinumab; EXP, 75mg secukinumab + verbal suggestion.

With regard to itch, there was a significant effect of group (F = 5.33, p = 0.006), driven by higher values in the EXP group. DLQI scores did not show a significant group effect (F = 1.53, p = 0.221), but there was a significant interaction effect indicating a less steep decline in symptoms in the EXP group compared to the other groups (F = 6.38, p = 0.002). At week 16, 67% of patients in the TAU group achieved a DLQI 0/1 and 81% a P-VAS improvement of ≥4 points. In the EXP group, these responses were shown by 53% and 58% respectively and in the DC group by 42% and 77%. The comparison of AUCs revealed a significant advantage of the TAU compared to the EXP group for both outcomes and no statistically significant differences between EXP and DC groups (see Tables 2 and 3 for details).

## Secondary Outcomes

The analysis of IL-17A levels in patients' blood plasma revealed a significant increase over time (F = 9.72, p = 0.002), as shown in Figure 4. The groups did not differ significantly in IL-17A levels, and there was no interaction of time and group (refer to Table 4 for details). The assessment of mood as a secondary outcome showed a significant decrease in depressive symptoms over time (F = 57.70, p < 0.001). Moreover, there was a significant interaction effect, stemming from steeper

**Table 3** Clinically Meaningful Outcomes

| Outcome | Group | N | Patients with Response at Week 16 | | Test Statistic | Signifi cance | Effect Size |
|---|---|---|---|---|---|---|---|
| PASI75 | TAU | 36 | 77.78% | Main effect of group | F = 6.84 | p = 0.002 | |
| | DC | 36 | 38.89% | | | | |
| | EXP | 34 | 50.00% | Post-hoc comparisons | | | |
| | | | | TAU vs DC<br>TAU vs EXP<br>DC vs EXP | t = −3.55<br>t = −2.49<br>t = 0.99 | p < 0.001<br>p = 0.015<br>p = 0.324 | d = −0.837<br>d = −0.596<br>d = 0.238 |
| DLQI 0/1 | TAU | 36 | 66.67% | Main effect of group | F = 4.40 | p = 0.015 | |
| | DC | 36 | 41.67% | | | | |
| | EXP | 34 | 52.94% | Post-hoc comparisons | | | |
| | | | | TAU vs DC<br>TAU vs EXP<br>DC vs EXP | t = −2.89<br>t = −2.16<br>t = 0.58 | p = 0.005<br>p = 0.034<br>p = 0.566 | d = −0.681<br>d = −0.518<br>d = 0.138 |
| P-VAS ≥4-point improve ment | TAU | 20 | 80.95% | Main effect of group | F = 3.77 | p = 0.028 | |
| | DC | 22 | 77.27% | | | | |
| | EXP | 26 | 57.69% | Post-hoc comparisons | | | |
| | | | | TAU vs DC<br>TAU vs EXP<br>DC vs EXP | t = −1.43<br>t = −2.68<br>t = −1.36 | p = 0.160<br>p = 0.010<br>p = 0.181 | d = −0.437<br>d = −0.781<br>d = −0.391 |

**Notes**: For the analysis of itch improvement, all patients with less than 4 points itch at baseline were excluded (n = 42). Effect size is given as Cohen's d.
**Abbreviations**: PASI, Psoriasis Area and Severity Index; DLQI, Dermatology Life Quality Index; TAU, Treatment as usual with 300mg secukinumab; DC, Dose control with 75mg secukinumab; EXP, 75mg secukinumab + verbal suggestion.

decline in the TAU group compared to the EXP group (F = 12.56, p < 0.001, mean score reduction: TAU = 3.7, EXP = 1.8). Anxiety symptoms also decreased significantly over time (F = 177.34, p < 0.001), with a notable interaction effect of time and group (F = 8.34, p < 0.001), indicating a steeper decline in the TAU group and in the EXP group compared to the DC group.

**Table 4** Mixed Model Results of Secondary Outcomes

| Dependent Variable | Group | N | Effect | Test Statistic | Significance | Likelihood Ratio |
|---|---|---|---|---|---|---|
| IL-17A levels | TAU | 39 | Intercept | F = 45.84 | p < 0.001 | |
| | DC | 35 | Time (main effect) | F = 11.65 | p = 0.001 | 14.94 |
| | EXP | 39 | Group (main effect)<br>a. EXP vs DC<br>a. EXP vs TAU | F = 0.15<br>t = −0.31<br>t = −0.26 | p = 0.860<br>p = 0.757<br>p = 0.793 | 16.27 |
| | | | Time*Group (interaction)<br>a. Time* EXP vs DC<br>a. Time* EXP vs TAU | F = 0.01<br>t = 0.07<br>t = −0.05 | p = 0.993<br>p = 0.945<br>p = 0.961 | 10.05 |

(*Continued*)


https://doi.org/10.2147/PTT.S486338

**Table 4** (Continued).

| Dependent Variable | Group | N | Effect | Test Statistic | Significance | Likelihood Ratio |
|---|---|---|---|---|---|---|
| STADI State Depression | TAU | 40 | Intercept | F = 2447.26 | p < 0.001 | |
| | DC | 39 | Time (main effect) | F = 57.70 | p < 0.001 | 49.71 |
| | EXP | 39 | Group (main effect)<br>a. EXP vs DC<br>a. EXP vs TAU | F = 0.58<br>t = 0.42<br>t = 1.77 | p = 0.559<br>p = 0.677<br>p = 0.080 | 4.35 |
| | | | Time*Group (interaction)<br>a. Time* EXP vs DC<br>a. Time* EXP vs TAU | F = 12.56<br>t = 0.60<br>t = −3.97 | p < 0.001<br>p = 0.551<br>p < 0.001 | 18.91 |
| STADI State Anxiety | TAU | 40 | Intercept | F = 2142.03 | p < 0.001 | |
| | DC | 39 | Time (main effect) | F = 177.34 | p < 0.001 | 152.97 |
| | EXP | 39 | Group (main effect)<br>a. EXP vs DC<br>a. EXP vs TAU | F = 1.19<br>t = 0.24<br>t = 1.57 | p = 0.308<br>p = 0.808<br>p = 0.120 | 5.06 |
| | | | Time*Group (interaction)<br>a. Time* EXP vs DC<br>a. Time* EXP vs TAU | F = 8.34<br>t = 1.93<br>t = −2.11 | p < 0.001<br>p = 0.054<br>p = 0.035 | 10.68 |

**Notes**: Likelihood ratio = likelihood of the data comparing a model including a given effect to a model including only the mean of the outcome variable, thereby illustrating the added benefit provided by each variable as a measure of effect size. * denotes a multiplication, ie separates the factors underlying the interaction effect.

**Abbreviations**: IL, Interleukin, measured in pg/mL; TAU, Treatment as usual with 300mg secukinumab; DC, Dose control with 75mg secukinumab; EXP, 75mg secukinumab + verbal suggestion.

## Adverse Events

A full list of reported adverse events (AEs) can be found in supplementary Table 4. The safety profile was consistent with prior studies on secukinumab and none of the serious AEs were suspected to be treatment-related. Due to the low numbers of AEs that were suspected to be treatment-related, no statistical comparison of groups was conducted.

## Explanatory Variables

To analyze potential effects of gender, BMI and age, these variables were included as covariates in the linear mixed models. After FDR-correction for multiple comparisons, there were no significant main or interaction effects with regard to gender. Higher BMI led to higher symptom burden in PASI and DLQI and increased the differences between TAU and the dose-reduced groups when it came to itch. Irrespective of group, younger patients displayed more pronounced improvement over time in all three outcomes. Details of the statistical analyses can be found in supplementary Table 5.

# Discussion

The presented study aimed to enhance treatment expectations of patients with psoriasis to improve the effectiveness of low-dose systemic anti-psoriatic therapy with the IL-17A antagonist secukinumab. Patients were randomized to three groups, receiving either treatment as usual or a dose reduction of 75%. Verbal suggestion of probable treatment success supported by a gustatory stimulus was used to heighten expectations in one low dose group.

While all three groups showed symptom improvement over the treatment period of four months, the TAU group was superior in achieving clinically meaningful change (PASI, DLQI, itch). At the same time, there were no clinically meaningful differences between the two dose-reduced groups in none of the three primary outcomes. Over time, the EXP-group showed faster decline in PASI scores compared to the DC-group but less improvement in quality of life. Despite the 75% reduction in dosage there was no difference in plasma IL-17A concentrations, which increased in all

groups upon treatment initiation. Depressive and anxiety symptoms significantly decreased over the treatment period in all groups, with a slightly steeper decline in depressive symptoms in the TAU group and reduced anxiety in TAU and EXP groups compared to the DC group.

Past research shows that verbal suggestion can influence treatment expectations and reduce symptoms like pain[7] and itch[43] and enhance medication effectiveness.[44] As many results so far come from pain studies, the generalizability to a field with differing pathophysiological background needs to be carefully tested. In dermatology, there is evidence for the importance of verbal suggestion and associative learning, as seen in allergy research.[15,45] So far, however, only a single other study has experimentally explored placebo effects in patients suffering from psoriasis.[14] Adding to this small body of research, our study found that verbal suggestion alone is probably not sufficient to ameliorate symptoms in this cohort, corroborating earlier dermatological findings.[46,47]

Some studies indicate that associative learning could be a stronger driver of positive expectations,[48] and combining it with verbal suggestion often produces significant placebo effects.[13,49] Moreover, the effectiveness of placebo treatments may depend on the type of outcome: One study in patients suffering from asthma for example found no difference between placebo and no treatment in expiratory volume. At the same time, placebo and active treatment had comparable effects on patient-reported symptom improvement.[50] Similar observations in other cohorts have led to the idea that patient-reported outcomes can be influenced by mere verbal suggestion, while objectively measured outcomes like changes in hormone concentrations or immune cell counts need prior experiences, ie associative learning for placebo interventions to be successful.[12,51]

The presented study, however, could not find striking differences between patient-reported and physician-assessed outcomes. A potential explanation for this inconsistency could be the fact that prior experimental studies have typically looked into acute symptoms. In a longitudinal setting such as the one employed here, subjective and objective symptoms, like quality of life and observable skin symptoms, may be more closely linked.

The assessment of patients' treatment expectations showed that these were already on a high level at baseline (8.1 of 10 points), indicating a ceiling effect. Consequently, the experimental manipulation was not successful at further increasing these expectations. Given the setting in a modern university hospital specialized in psoriasis treatment and the option to receive a novel and highly effective treatment with a monoclonal antibody, it is possible that the verbal suggestions by the treating physician were in comparison insufficient to further increase treatment expectations.

The results also show that 25% of the usual dose of secukinumab may already lead to significant symptom improvement and an increase in IL-17A levels similar to that observed in the TAU group. This mirrors what has been seen in a phase-II dose-finding study in a small group of patients (N = 25)[52] and provides the first real-world evidence for the effects of the 75mg dosage. Considering the immense costs associated with long-term biologic treatment,[53] this finding is interesting from an economical perspective: currently the yearly costs of secukinumab treatment amount to approximately 18.600€ or $20.150 per year once the induction phase has been completed[54] and the application of lower dosages could make this type of treatment available to more people globally.

## Strengths and Limitations

A clear strength of this study is its ecological validity, with a setting and procedures that are close to clinical routine. This notion was further promoted by the inclusion of a diverse sample, not excluding any patients based on their demographic information. At the same time, however, this ecological validity comes with certain drawbacks, like the baseline differences in BMI and PASI score seen in our experimental groups. Their starting with a higher burden of skin symptoms may have influenced the treatment trajectories of the EXP group and presents a potential source of bias. While stratification of baseline characteristics is a valuable option that should be considered in future studies, there are certainly limits to the feasibility of this method.

## Future Directions

An interesting route for the future could be the employment of other strategies to harness the placebo effect in this type of treatment. Expectations may have been too high to be raised any further by verbal manipulation, but this may be achieved by other methods, like social observation[55] or associative learning.[56,57] While associative learning has already been tested

successfully in a pilot study with psoriasis patients under topical treatment,[14] social learning as a method for symptom relief has – to our knowledge – not been studied in dermatological patients so far.

## Conclusion

Taken together, the presented results indicate that the mere verbal suggestion of treatment success might be insufficient to shape positive treatment expectations in psoriasis patients in the context of already high expectations. However, they also illustrate the feasibility of the employed model to study placebo effects in this cohort: the reduced dosage was still sufficient to elicit symptom improvement, which is an important ethical consideration when designing such studies and other mechanisms like associative learning or social observation could be tested in a similar design. The advancement of such approaches could on the one hand improve clinical care, by achieving the same treatment success while reducing the amount of medication intake necessary. On the other hand, an exploration of placebo effects in patients suffering from an inflammatory disease like psoriasis can generate important insights into the generalizability of a field that has mostly grown in the domain of pain.

## Data Sharing Statement

De-identified participant data will be made openly available upon publication via the Open Science Framework (OSF). This will include all data relevant to the analyses and findings presented within this work.

## Acknowledgments

We thank Felix Testroet and Lea Schneider for their support in the administration and collection of data for this study. We also thank our stand-in study physicians Lea Jessica Albrecht, Katharina Baratella, Rosa Iliasian, Monika Kleinhans, Fiona Koch, and Anne-Christine Müseler, as well as all blinded raters who assessed PASI scores for this study. Finally, we want to thank our patients, who entrusted us with accompanying them on their treatment journey.

## Funding

Gefördert durch die Deutsche Forschungsgemeinschaft (DFG)—Projektnummer 422744262—TRR 289—Funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation)—Project-ID 422744262—TRR 289.

## Disclosure

SH, SM and DB report no conflict of interest. Frederik Krefting received travel support for participation in congresses and / or (speaker) honoraria from Novartis, Lilly, Bristol-Myers Squibb, Janssen, Almirall, and Boehringer Ingelheim outside of the present publication. MS reports speaker honoraria from Lilly, Allergopharma, NovoNordisk, Sanofi, Janssen, InVo, Bristol-Meyers, NCO, Almirall, and Berlin Chemie. WS reports grants and/or travel support and/or personal fees and/or speaker honoraria from medi GmbH Bayreuth, AbbVie, Almirall, Amgen, Bristol-Myers Squibb, Celgene, GSK, Janssen, LEO Pharma, Lilly, MSD, Novartis, Pfizer, Roche, Sanofi Genzyme, and UCB outside the submitted work.

The authors report no other conflicts of interest in this work.

## References

1. Schedlowski M, Enck P, Rief W, Bingel U. Neuro-bio-behavioral mechanisms of placebo and nocebo responses: implications for clinical trials and clinical practice. *Pharmacol Rev*. 2015;67(3):697–730. doi:10.1124/pr.114.009423
2. Benedetti F. Placebo and the new physiology of the doctor-patient relationship. *Physiol Rev*. 2013;93(3):1207–1246. doi:10.1152/physrev.00043.2012
3. Evers AWM, Colloca L, Blease C, et al. What should clinicians tell patients about placebo and nocebo effects? Practical considerations based on expert consensus. *Psychother Psychosom*. 2021;90(1):49–56. doi:10.1159/000510738
4. Bingel U. Placebo 2.0: the impact of expectations on analgesic treatment outcome. *Pain*. 2020;161(Suppl 1):S48–s56. doi:10.1097/j.pain.0000000000001981
5. Wager TD, Atlas LY. The neuroscience of placebo effects: connecting context, learning and health. *Nat Rev Neurosci*. 2015;16(7):403–418. doi:10.1038/nrn3976
6. Hölsken S, Schedlowski M, Hadamitzky M, Heiss-Lückemann L. Learned immune responses. In: LJN C, Franklin PD, Seneviratne C, editors. *Placebo Effects Through the Lens of Translational Research*. New York, USA: Oxford University Press; 2023:147–162.
7. Colloca L. The placebo effect in pain therapies. *Ann Rev Pharmacol Toxicol*. 2019;59(1):191–211. doi:10.1146/annurev-pharmtox-010818-021542

8. Kirsch I. Placebo effect in the treatment of depression and anxiety. *Front Psychiatry*. 2019;10:407. doi:10.3389/fpsyt.2019.00407
9. Andreasen TH, Christensen MO, Halling AS, Egeberg A, Thyssen JP. Placebo response in Phase 2 and 3 trials of systemic and biologic therapies for atopic dermatitis - a systematic review and meta-analysis. *J Eur Acad Dermatol Venereol*. 2019;34(6):1143–1150.
10. van Laarhoven AI, van der Sman-Mauriks IM, Donders ART, Pronk MC, van de Kerkhof PCM, Evers AWM. Placebo effects on itch: a meta-analysis of clinical trials of patients with dermatological conditions. *J Invest Dermatol*. 2015;135(5):1234–1243. doi:10.1038/jid.2014.522
11. Vits S, Cesko E, Benson S, et al. Cognitive factors mediate placebo responses in patients with house dust mite allergy. *PLoS One*. 2013;8(11): e79576. doi:10.1371/journal.pone.0079576
12. Goebel MU, Meykadeh N, Kou W, Schedlowski M, Hengge UR. Behavioral conditioning of antihistamine effects in patients with allergic rhinitis. *Psychother Psychosom*. 2008;77(4):227–234. doi:10.1159/000126074
13. Sölle A, Worm M, Benedetti F, Sabine Bartholomaus T, Schwender-Groen L, Klinger R. Targeted use of placebo effects decreases experimental itch in atopic dermatitis patients: a randomized controlled trial. *Clin Pharmacol Ther*. 2021;110(2):486–497. doi:10.1002/cpt.2276
14. Ader R, Mercurio MG, Walton J, et al. Conditioned pharmacotherapeutic effects: a preliminary study. *Psychosom Med*. 2010;72(2):192–197. doi:10.1097/PSY.0b013e3181cbd38b
15. Sondermann W, Reinboldt-Jockenhöfer F, Dissemond J, Pfaar O, Bingel U, Schedlowski M. Effects of patients' expectation in dermatology: evidence from experimental and clinical placebo studies and implications for dermatologic practice and research. *Dermatology*. 2021;237:1–15.
16. Ayasse MT, Buddenkotte J, Alam M, Steinhoff M. Role of neuroimmune circuits and pruritus in psoriasis. *Exp Dermatol*. 2020;29(4):414–426. doi:10.1111/exd.14071
17. Griffiths CEM, Armstrong AW, Gudjonsson JE, Barker J. Psoriasis. *Lancet*. 2021;397(10281):1301–1315. doi:10.1016/S0140-6736(20)32549-6
18. Armstrong AW, Mehta MD, Schupp CW, Gondo GC, Bell SJ, Griffiths CEM. Psoriasis prevalence in adults in the United States. *JAMA Dermatol*. 2021;157(8):940–946. doi:10.1001/jamadermatol.2021.2007
19. Sewerin P, Brinks R, Schneider M, Haase I, Vordenbaumen S. Prevalence and incidence of psoriasis and psoriatic arthritis. *Ann Rheum Dis*. 2019;78(2):286–287. doi:10.1136/annrheumdis-2018-214065
20. Lynde CW, Poulin Y, Vender R, Bourcier M, Khalil S. Interleukin 17A: toward a new understanding of psoriasis pathogenesis. *J Am Acad Dermatol*. 2014;71(1):141–150. doi:10.1016/j.jaad.2013.12.036
21. Rendon A, Schäkel K. Psoriasis pathogenesis and treatment. *Int J Mol Sci*. 2019;20(6):1475. doi:10.3390/ijms20061475
22. Blauvelt A, Shi N, Zhu B, et al. Comparison of health care costs among patients with psoriasis initiating ixekizumab, secukinumab, or adalimumab. *J Manag Care Spec Pharm*. 2019;25(12):1366–1376. doi:10.18553/jmcp.2019.25.12.1366
23. Nast A, Altenburg A, Augustin M, et al. Deutsche S3-Leitlinie zur Therapie der Psoriasis vulgaris, adaptiert von EuroGuiDerm - Teil 2: Therapiemonitoring, besondere klinische Situationen und Komorbidität[German S3 guideline for the treatment of psoriasis vulgaris, adapted from EuroGuiDerm - Part 2: Therapy monitoring, special clinical situations and comorbidity]. *J Dtsch Dermatol Ges*. 2021;19(7):1092–1117 German.
24. Nast A, Smith C, Spuls PI, et al. EuroGuiDerm Guideline on the systemic treatment of Psoriasis vulgaris - Part 1: treatment and monitoring recommendations. *J Eur Acad Dermatol Venereol*. 2020;34(11):2461–2498. doi:10.1111/jdv.16915
25. Hölsken S, Krefting F, Schedlowski M, Sondermann W. Expectation-induced enhancement of pain, itch and quality of life in psoriasis patients: study protocol of a randomised controlled trial. *BMJ Open*. 2021;11(9):e047099. doi:10.1136/bmjopen-2020-047099
26. CRC 289 Treatment Expectation, Essen, Germany. Available from: https://treatment-expectation.de. Accessed December 16, 2024.
27. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *J Clin Epidemiol*. 2010;63(8):e1–37. doi:10.1016/j.jclinepi.2010.03.004
28. European Medicines Agency. Cosentyx: EPAR - Product Information. 2023. Available from: https://www.ema.europa.eu/en/documents/product-information/cosentyx-epar-product-information_en.pdf. Accessed December 16, 2024.
29. Fredriksson T, Pettersson U. Severe psoriasis--oral therapy with a new retinoid. *Dermatologica*. 1978;157(4):238–244. doi:10.1159/000250839
30. Schmitt J, Wozel G. The psoriasis area and severity index is the adequate criterion to define severity in chronic plaque-type psoriasis. *Dermatology*. 2005;210(3):194–199. doi:10.1159/000083509
31. Bozek A, Reich A. The reliability of three psoriasis assessment tools: psoriasis area and severity index, body surface area and physician global assessment. *Adv Clin Exp Med*. 2017;26(5):851–856. doi:10.17219/acem/69804
32. Englert R, Schedlowski M, Engler H, et al. *ALIIAS*: anonymization with limesurvey integration and II-factor authentication for scientific research. *SSRN Electronic Journal*. 2022. doi:10.2139/ssrn.4089108
33. Kirchhof J, Petrakova L, Brinkhoff A, et al. Learned immunosuppressive placebo responses in renal transplant patients. *Proc Natl Acad Sci*. 2018;115(16):4223–4227. doi:10.1073/pnas.1720548115
34. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. *Clin Exp Dermatol*. 1994;19 (3):210–216. doi:10.1111/j.1365-2230.1994.tb01167.x
35. Laux L, Hock M, Bergner-Köther R, Hodapp V, Renner KH, inventorStadi: state-trait-angst-depressions-inventar.2013.
36. Mrowietz U, Kragballe K, Reich K, et al. Definition of treatment goals for moderate to severe psoriasis: a European consensus. *Arch Dermatol Res*. 2011;303(1):1–10. doi:10.1007/s00403-010-1080-1
37. Rief W, Nestoriuc Y, Mueller EM, Hermann C, Schmidt K, Bingel U Generic rating scale for previous treatment experiences, treatment expectations, and treatment effects (GEEE). PsychArchives; 2021.
38. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods*. 2007;39(2):175–191. doi:10.3758/BF03193146
39. Team RC. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2022.
40. Pinheiro J; R Core Team. nlme: linear and nonlinear mixed effects models. *R Package Version*. 2011;3:1–164ed2023.
41. Wickham H. *ggplot2: Elegant Graphics for Data Analysis*. Springer-Verlag New York; 2009.
42. Pruessner JC, Kirschbaum C, Meinlschmid G, Hellhammer DH. Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. *Psychoneuroendocrinology*. 2003;28(7):916–931. doi:10.1016/S0306-4530(02)00108-7
43. Meeuwis SH, van Middendorp H, van Laarhoven AIM, et al. Placebo and nocebo effects for itch and itch-related immune outcomes: a systematic review of animal and human studies. *Neurosci Biobehav Rev*. 2020;113:325–337. doi:10.1016/j.neubiorev.2020.03.025

44. Bingel U, Wanigasekera V, Wiech K, et al. The effect of treatment expectation on drug efficacy: imaging the analgesic benefit of the opioid remifentanil. *Sci Transl Med*. 2011;3(70):70ra14. doi:10.1126/scitranslmed.3001244
45. Pfaar O, Agache I, Bergmann KC, et al. Placebo effects in allergen immunotherapy-An EAACI task force position paper. *Allergy*. 2021;76 (3):629–647. doi:10.1111/all.14331
46. Vits S, Dissemond J, Schadendorf D, et al. Expectation-induced placebo responses fail to accelerate wound healing in healthy volunteers: results from a prospective controlled experimental trial. *Int Wound J*. 2015;12(6):664–668. doi:10.1111/iwj.12193
47. Jockenhöfer F, Knust C, Benson S, Schedlowski M, Dissemond J. Influence of placebo effects on quality of life and wound healing in patients with chronic venous leg ulcers. *J Dtsch Dermatol Ges*. 2020;18(2):103–109. doi:10.1111/ddg.13996
48. Colloca L, Benedetti F. How prior experience shapes placebo analgesia. *Pain*. 2006;124(1–2):126–133. doi:10.1016/j.pain.2006.04.005
49. Bartels DJ, van Laarhoven AI, Haverkamp EA, et al. Role of conditioning and verbal suggestion in placebo and nocebo effects on itch. *PLoS One*. 2014;9(3):e91727. doi:10.1371/journal.pone.0091727
50. Wechsler ME, Kelley JM, Boyd IO, et al. Active albuterol or placebo, sham acupuncture, or no intervention in asthma. *N Engl J Med*. 2011;365 (2):119–126. doi:10.1056/NEJMoa1103319
51. Benedetti F, Pollo A, Loplano L, Lanotte M, Vighetti S, Rainero I. Conscious expectation and unconscious conditioning in analgesic, motor, and hormonal placebo/nocebo responses. *J Neurosci*. 2003;23(10):4315–4323. doi:10.1523/JNEUROSCI.23-10-04315.2003
52. Papp KA, Langley RG, Sigurgeirsson B, et al. Efficacy and safety of secukinumab in the treatment of moderate-to-severe plaque psoriasis: a randomized, double-blind, placebo-controlled Phase II dose-ranging study. *Br J Dermatol*. 2013;168(2):412–421. doi:10.1111/bjd.12110
53. Wu JJ, Feldman SR, Rastogi S, Menges B, Lingohr-Smith M, Lin J. Comparison of the cost-effectiveness of biologic drugs used for moderate-to-severe psoriasis treatment in the United States. *J DermatolTreat*. 2018;29(8):769–774. doi:10.1080/09546634.2018.1466022
54. ifap. Service-Institut für Ärzte und Apotheker GmbH[Service Institute for Doctors and Pharmacists GmbH]. 2024. Available from: https://www.ifap.de/. Accessed December 16, 2024.
55. Schenk LA, Krimmel SR, Colloca L. Observe to get pain relief: current evidence and potential mechanisms of socially learned pain modulation. *Pain*. 2017;158(11):2077–2081. doi:10.1097/j.pain.0000000000000943
56. Colloca L, Miller FG. How placebo responses are formed: a learning perspective. *Philos Trans R Soc London Ser B*. 2011;366(1572):1859–1869. doi:10.1098/rstb.2010.0398
57. Hadamitzky M, Schedlowski M. Harnessing associative learning paradigms to optimize drug treatment. *Trends Pharmacol Sci*. 2022;43 (6):464–472. doi:10.1016/j.tips.2022.03.002