PAIN

The effects of treatment failure generalize across different routes of drug administration

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Failure of medical treatments can hamper responses to subsequent treatments. It has been suggested that changing the route of drug administration could reduce such negative carry-over effects, but direct evidence for this approach is lacking. We therefore investigated in 211 healthy volunteers whether changes in drug administration route reduce such carry-over effects. A positive or negative treatment history with topical analgesic treatments was induced experimentally in a mock clinical trial setting. Subsequently, a different inert drug was introduced via the same (topical) or another (oral) route of administration and its analgesic efficacy was tested. Changing the route of drug administration induced expectations of positive treatment effects in the subjects but did not actually counteract the negative carry-over effects on treatment efficacy. These findings indicate that learned carry-over effects generalize over time and across routes of drug administration—independent of conscious expectations. Other strategies are needed to prevent negative carry-over effects of treatment failure from influencing the results of subsequent treatment attempts.

INTRODUCTION

Patients' experience with previous treatments (their treatment history) can markedly influence therapeutic outcomes (*1*, *2*). This has been shown in clinical trials, where negative carry-over effects from ineffective treatments were observed (*3*–*5*). Patients with a history of unsuccessful treatments showed smaller treatment responses than treatment-naïve patients (*3*, *6*–*9*). These clinical observations have been substantiated experimentally: Influence of treatment history transfers over time and over therapeutic approaches (*10*, *11*). A negative treatment history diminished the analgesic efficacy of a different analgesic treatment at the behavioral and neurobiological level. Such negative carry-over effects of treatment history have important implications for medical practice and the design of clinical trials. They are particularly likely to influence chronic conditions in which treatment attempts often repeatedly fail and negative treatment experiences accumulate, which in turn hamper responses to future treatments. It would therefore be desirable to systematically reduce negative and increase positive carry-over effects of treatment history.

Carry-over effects are thought to be mediated, at least in part, via associative learning (*12*). It is a well-known phenomenon in associative learning that learned associations can generalize to similar stimuli (*13*). Carry-over effects should therefore be stronger when treatments are more similar. Conversely, the more different the treatments are, the weaker the carry-over effects should be. On the basis of this logic, a change in treatment features should reduce the negative carry-over effects of treatment history. A change in the route of drug administration (RoA), for instance, which includes a change in the appearance of the drug and in its application, might be a powerful strategy to overcome this unwanted transfer. Besides an effect on learned associations, a change in treatment features might also revive treatment expectations, which have been shown to affect treatment outcome (*14*).

Here, we addressed these hypotheses experimentally by pooling data from six substudies in healthy human participants. We chose an experimental approach because one cannot deliberately expose patients to treatment failure, and assessing treatment history effects in a prospective clinical study is therefore limited. To investigate our hypothesis irrespective of any pharmacological peculiarities or other confounding factors present in clinical practice, we induced a positive or negative treatment history with a topical analgesic treatment in a mock clinical trial setting. The presence or absence of a treatment effect was simulated experimentally for 2 days (conditioning session). On the third day, we introduced a different inert drug either via the same (topical) or via another (oral) RoA and tested its analgesic efficacy. Treatment effects were defined as analgesic responses in an experimental heat pain model using pain intensity ratings.

RESULTS

Study participants

A total of 211 participants (47.4% male; mean age, 26 years; range, 19 to 36 years) from six substudies were included in the study, and another 25 participants were excluded (for details, see fig. S1). Three further participants had to be excluded from analysis of pain ratings because heat stimulus temperatures were not recorded. Each participant was assigned to one of four groups: group 1, positive treatment experience (no change in RoA); group 2, negative treatment experience (no change in RoA); group 3, positive treatment experience (change in RoA); and group 4, negative treatment experience (change in RoA) (for details, see Fig. 1 and table S1).

The effect of treatment history and RoA change on treatment expectations

First, we tested how an individual's treatment experience during the conditioning session and the RoA change shaped the treatment expectations toward the novel treatment on day 3. Our results show that the participants' treatment expectations changed over the course of the experiment (fig. S2A). Before day 1, all groups indicated similar treatment expectations, corresponding to a moderate analgesic effect of 51.9 visual analog scale (VAS) units [mean; 95% confidence interval (CI),

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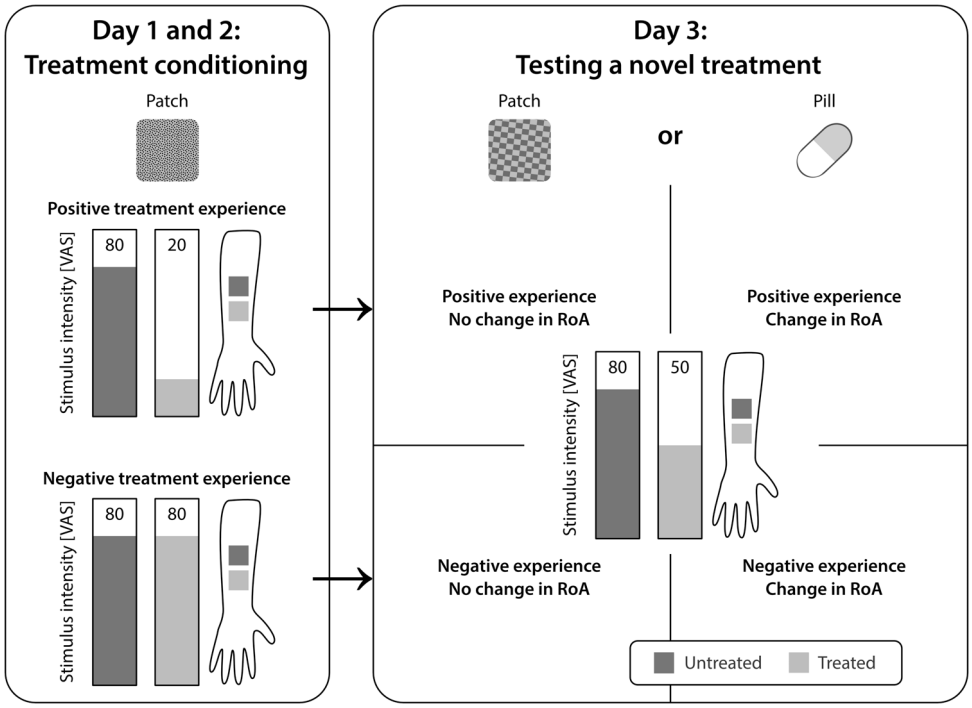

Fig. 1. Experimental design. The experiment took place on three consecutive days. On days 1 and 2, either a positive or negative treatment experience was induced by combining an inert patch treatment with a conditioning procedure. On day 3, the analgesic response to a second analgesic treatment applied via the same (ointment applied via patch) or another (pill) RoA was assessed. Bars indicate the stimulation intensities of applied heat pain stimuli in VAS units.

49.0 to 54.9]. As expected, the positive and negative groups started to diverge on day 2: The negative experience groups, which had no analgesic effect during the conditioning sessions, showed markedly lowered average treatment expectations compared to day 1 [mean, 22.3 VAS units; 95% CI, 18.2 to 26.9), whereas the positive experience groups, which had an analgesic effect during the conditioning session, expressed increased expectations (mean, 71.6 VAS units; 95% CI, 67.4 to 75.3). Announcement of the novel treatment on day 3 significantly increased treatment expectations obtained before the actual treatment in the negative experience groups (paired t test; +24.4 VAS units; 95% CI, 19.5 to 29.2; $t_{95} = 10.1$; $P < 0.001$) but significantly decreased treatment expectations in the positive experience groups (paired t test; −10.7 VAS units; 95% CI, −6.6 to −14.7; $t_{103} = 5.19$; $P < 0.001$) in comparison to day 2.

A general linear model (GLM) analysis (table S2, left) revealed that treatment expectation on day 3 was significantly affected by treatment experience ($F_{1,\ 192} = 21.3$; $\eta^2 = 0.088$; $P < 0.001$) and that RoA change modulated this effect of treatment experience ($F_{1,\ 192} = 19.0$; $\eta^2 = 0.079$; $P < 0.001$) (Fig. 2A). Changing the RoA on day 3 led to a mean increase of treatment expectations in the negative group by 17.8 VAS units (95% CI, 6.6 to 29.0) but decreased it in the positive groups (mean, −8.3 VAS units; 95% CI, −19.3 to 2.80). There was no main effect of RoA change on treatment expectations ($F_{1,\ 192} = 0.59$; $\eta^2 = 0.002$; $P = 0.442$). Full results for the GLM analysis are shown in table S2 (left).

The effect of treatment history and RoA change on treatment outcomes

Next, we investigated whether conditioning successfully induced the intended positive or negative treatment experiences. As shown in fig. S2 (B to E), temperatures applied during the two conditioning sessions on days 1 and 2 led to pain ratings that were close to the desired target values (no pain relief in the negative treatment history group and a pain relief of 60 VAS units in the positive group). To this end, the negative treatment group received the same high individually calibrated temperatures at both the untreated control (mean, 46.9°C; fig. S2B, blue) and the treatment site (mean, 46.9°C; fig. S2C, blue), resulting in pain ratings of about 80 VAS units (fig. S2E, blue). As intended, the negative treatment experience group therefore showed a mean treatment effect close to 0 on conditioning days 1 and 2 (mean pain ratings of control minus treatment, 1.18 VAS units; 95% CI, −0.25 to 2.90). The positive experience groups received high temperatures at the control (mean, 47.2°C; fig. S2B, red) but lowered temperatures at the treatment site (mean, 45.0°C; fig. S2C, red), leading to pain ratings of about 80 and 20 VAS units, respectively (fig. S2, D and E, red). As intended, the positive treatment experience group therefore showed a mean treatment effect of about 60 VAS units (57.4 VAS units; 95% CI, 54.9 to 59.7; across days 1 and 2).

On day 3, all groups received high temperatures at the control site (mean, 47.1°C; fig. S2B), targeting a pain rating of 80 VAS units, and slightly lowered temperatures at the treatment site (46.2°C; fig. S2C), targeting a pain rating of 50 VAS units (fig. S2D). We then tested how treatment experience on days 1 and 2 and RoA change influenced the analgesic treatment outcome (indexed by the difference in VAS pain ratings between the treatment and control sites). This GLM analysis controlled for study differences, as well as differences in applied temperatures. We found a significant main effect of treatment experience on analgesic treatment outcome ($F_{1,\ 198} = 12.4$; $\eta^2 = 0.052$; $P = 0.0005$) (Fig. 2B). The analgesic treatment effect in the negative compared to the positive group was reduced by a mean of −5.8 VAS units (95% CI, −10.9 to −0.69). We found no main effect of RoA change on treatment outcome ($F_{1,\ 198} = 2.25$; $\eta^2 = 0.009$; $P = 0.135$), and RoA did not significantly counteract the treatment history effect ($F_{1,\ 198} = 0.46$; $\eta^2 = 0.002$; $P = 0.499$). Full results for the GLM analysis are shown in table S2 (right).

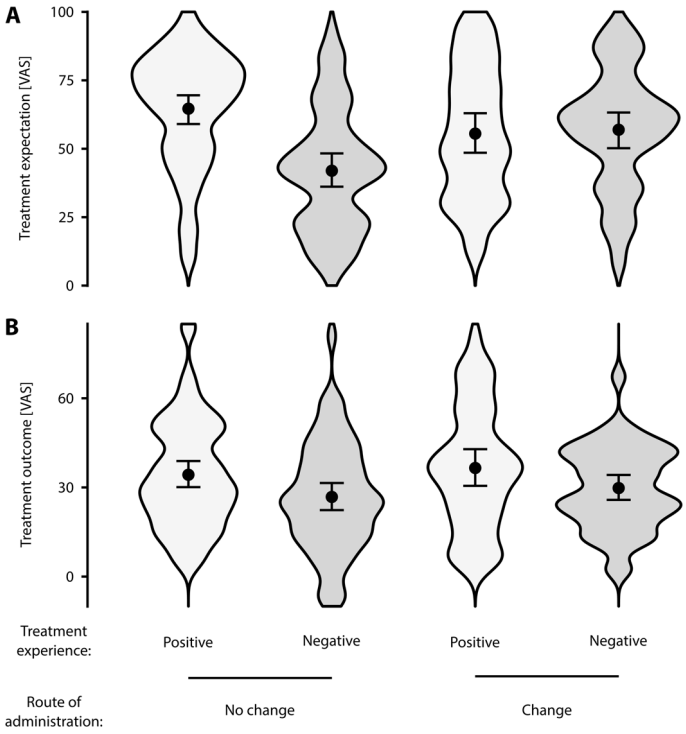

Fig. 2. Treatment expectations and treatment outcomes. (**A**) Treatment expectations on day 3 assessed on a VAS (0 to 100) (0, no pain relief; 100, complete pain relief) showed a significant main effect of treatment experience on treatment expectations (n = 199; P = 0.000007), as well as a significant interaction between treatment experience and RoA change (n = 199; P = 0.00002) in GLM analysis. (**B**) Treatment outcomes on day 3 indexed by the difference in pain ratings (VAS 0 to 100) (0, no pain; 100, unbearable pain) at the treatment site versus the control site are significantly influenced by previous treatment experience (n = 207; P = 0.0005), as evident in the reduced analgesic treatment effect in the negative treatment experience compared to the positive treatment experience groups. The change in RoA does not counteract this effect (n = 207; P = 0.499). All values shown were corrected for mean by-study differences; pain ratings were additionally corrected for individual temperature differences. (A) and (B) depict group means ± bootstrapped 95% CIs plotted on top of violin plots representing the probability density of the underlying data (kernel-smoothed with a bandwidth of 0.5 U).

Associations of treatment expectations and analgesic outcome

An additional GLM analysis was performed to explore the effect of treatment expectations on treatment outcome. To test whether expectations could explain additional variance in analgesic outcome and/or affect the variance explained by treatment experience, we repeated the GLM analysis described above, but this time, we added expectancy ratings as a covariate.

Overall, treatment expectations did not explain significant additional variance in analgesic treatment outcome on day 3 ($F_{1,\ 187}$ = 0.50; η^2 = 0.002; P = 0.480) and had no significant effect on other coefficient estimates. Figure S3 illustrates the lack of correspondence between treatment expectations and treatment responses on day 3 for all groups. Full results for the GLM analysis are shown in table S3.

Additional control analyses

We performed additional control analyses to confirm the validity of our results. A GLM analysis of temperatures applied on day 3 indicated small but statistically significant temperature differences between groups: The temperature difference between control and placebo sites was slightly larger in the positive group than in the negative group (+0.13°C; 95% CI, 0.01 to 0.25; $F_{1,\ 204}$ = 3.99; η^2 = 0.019; P = 0.047) and in groups with no RoA change (+0.14°C; 95% CI, 0.01 to 0.28; $F_{1,\ 204}$ = 3.99; η^2 = 0.019; P = 0.047). We therefore controlled for temperature differences in our main analysis by including temperature as a covariate to ensure that imbalances of calibrated stimulus intensities do not affect our main results.

An analysis of residuals indicated normal, homoscedastic residual distributions with no obvious outliers for all models tested. We found no study-specific differences in our main outcome measures (expectation ratings and analgesic treatment outcome), indicating that our key results were not driven by study-specific differences (see tables S2 and S3). Finally, the demographic variables age and gender as factors were not found to affect the main results significantly (see table S4).

DISCUSSION

Here, we experimentally investigated whether a change in RoA influences carry-over effects of treatment history on expectation for and efficacy of a subsequent treatment. Our results show that a change in RoA induced positive treatment expectations regarding the second treatment but did not counteract negative carry-over effects on treatment efficacy. Our findings therefore indicate that learned carry-over effects may generalize across RoAs—irrespective of positive treatment expectations.

Our study of a cohort of 211 healthy participants agrees with the findings of a previous study of 39 participants (*11*) on carry-over effects of treatment history on treatment outcome. It extends previous findings by providing evidence for a generalization of negative carry-over effects across different routes of drug administration. This finding is somewhat surprising because the change in administration route led to an increase in positive treatment expectations—an observation that substantiates anecdotal evidence indicating that "trying something new" after an unsuccessful treatment attempt often raises new hope for treatment success. Positive treatment expectations have been shown to influence treatment outcome in experimental (*14*, *15*) and clinical trials (*16*), and together with prior learning experiences, expectations are seen as key determinants of treatment outcome (*17*, *18*). Although the exact relationship between expectations and learning (and specifically negative treatment experiences) is a subject of debate, it seems reasonable to assume that positive expectations are lowered after treatment failure. However, if new information becomes available that suggests that the subsequent treatment might be more successful, positive expectations might become stronger and override the detrimental influence of the prior negative experience. Here, we tested whether a new route of "drug" administration would suffice to cause this change. Our data show that although expectations recovered, they did not counteract the effect of prior treatment experience.

This finding is noteworthy for the following reasons: First, it provides insights into the relative strength of the effects of expectations and learning on treatment outcomes. The literature on the influence of both factors commonly assumes that both contribute to the process that determines treatment outcome, but their integration (particularly when both factors pull in different directions, as in our case) has not been studied in great detail. Our findings indicate that negative carry-over effects are predominantly driven by associative learning processes (*19*, *20*). Whether this reflects a general dominance of an individual's own experiences over expectations based on verbal or written instructions or is specific to our experimental paradigm requires further investigation.

Second, in agreement with findings showing that associative learning can influence outcomes regardless of participant awareness (*19*–*21*), our findings suggest that conscious expectations (as, for instance, assessed in participants' ratings) might need to be differentiated from unconscious expectations (*22*). This suggestion is in line with a framework that proposes that multiple, sometimes conflicting, expectations may coexist in different hierarchical levels of the mind (*22*, *23*). Although participants indicated in their ratings that they expected the second treatment to be effective, they might unconsciously have had doubts. Previous research into the influence of expectations on perception indicates that confidence in one's own expectancy ratings is crucial (*24*). Similar measures might be useful here to disambiguate these two different components in future studies.

Our observations might have profound implications for medical practice. Treatment failure is a daily experience for patients and health care professionals. The experience of treatment failure can accumulate over the course of chronic diseases and can hamper the efficacy of new treatment strategies. Concerted effort is therefore needed to avoid and overcome negative treatment experiences. Prevention of negative treatment experiences seems to be the most promising strategy. Increasing physicians' awareness of treatment history effects on treatment outcomes is an essential first step toward this goal. Our findings also challenge the use of common step care approaches in which treatment failure at earlier steps is required to justify progression to next-in-line interventions (*25*). Our results indicate that such an approach might increase the risk of exposure to repeated treatment failure and its detrimental consequences. Treatment decisions should therefore also consider the potential costs of treatment failure, which have to be weighed against the maximal possible benefit from the envisaged treatment.

Nevertheless, given the large interindividual variability of treatment responses, even to gold standard treatments, patients and health care professionals will inevitably continue to experience treatment failure despite all efforts. How can carry-over effects of these negative treatment experiences be prevented during subsequent treatment attempts? The exploration of two issues could aid in answering this question: First, how different a subsequent treatment must be from the previous one needs to be determined to prevent previous experiences from transferring. Here, only the RoA was changed; other key aspects of the treatment context, such as the physician or the environment of the treatment, remained unchanged. Although it is unclear how different features of the treatment and treatment context contribute to the treatment experience as a whole, it is likely that the contribution varies among features and among patients. The identification of key determinants for an individual patient could help guide treatment decisions if a change in treatment becomes necessary.

Second, it should be explored how information about subsequent treatment has to be conveyed to increase its persuasiveness. Here, participants received only very limited instructions regarding the treatment introduced on day 3. It can be speculated that the positive treatment expectations induced by the change in RoA may have succeeded in counteracting the effects of prior experience if they had been enriched by additional verbal instructions from the physician. Despite the substantial clinical relevance of this question, basic experimental research has only started to shed light on interactions between associative learning and verbal instructions and why conscious expectations are sometimes strongly related to outcomes and unrelated in other cases. We hope that our study inspires future work to answer these questions and to explore strategies on how to target and overcome the negative effects of treatment failure. Note that our study also has important implications for the design and interpretation of clinical trials, particularly crossover studies, where patients receive different treatments or those in which enrollment is dependent even on previous treatment responses (*26*–*28*).

Although our experimental approach allowed us to investigate carry-over effects of negative treatment experiences in a controlled setting, it has several limitations. Because the approach is not representative of all clinical settings, the findings do not necessarily generalize to every clinical situation. Here, "treatment history" was limited to a period of 2 days, and treatment effects were focused on analgesia in an acute experimental heat pain model. Whether the observed effects also apply to more long-standing treatment histories of patients and to other treatment effects remains to be investigated. However, the experimental approach used in the present study allowed for an isolation of the effects of treatment history independent of disease- or treatment-specific peculiarities (such as pharmacological conditioning effects) (*2*, *29*). Furthermore, our findings obtained after a very brief modulation of treatment experience are likely to underestimate rather than overestimate the effects of negative treatment history in clinical scenarios. We specifically investigated the effects of a change in RoA from topical to oral application; it is unknown whether these effects generalize to all changes in RoA. Further studies are therefore needed to test whether our results generalize to clinical populations with actual medical treatments.

In summary, our study on the effects of treatment history provided crucial insights into the relevance of contextual treatment factors. Our results indicate that treatment history can strongly influence treatment expectations and affect treatment outcome. Changing the RoA may be an efficient way to guide patients' expectations after treatment failure but is not sufficient to neutralize negative carry-over effects of treatment history. Our findings therefore suggest that we need new strategies to avoid negative treatment experiences and to prevent and counteract negative carry-over effects.

MATERIALS AND METHODS

Study design

To investigate the effect of treatment experiences on the outcome of subsequent treatment in a controlled experimental setting, we simulated analgesic treatment effects in a sham pharmacological trial. Painful heat stimulation at the forearm with covertly lowered stimulus intensities was used to induce positive and negative treatment experiences, as described previously (*11*). Participants in all studies were asked to complete three experimental sessions on three consecutive days. Days 1 and 2 were used for conditioning, to induce either a negative or a positive treatment experience (*30*). Day 3 was used for testing the effects of the induced treatment experiences on participant responses to a novel treatment and eventually testing the effects of RoA change.

We conducted six studies to test the effects of the factors "treatment experience" (levels, positive or negative) and "RoA change" (levels, no change or with change) in a between-group design. Participants were randomly assigned to one of four experimental groups (see Fig. 1) by using a consecutively numbered list. Participants, but not experimenters, were blinded in respect to group allocation. For details regarding the sample characteristics in each study, see table S1. Two of the substudies (studies 2 and 3) were previously published (*10*, *11*, *31*) and accounted for 32.2% of the sample, whereas 67.8% of data stem from previously unpublished studies.

Participants

Across the six studies, 236 healthy volunteers were recruited at the University of Hamburg and the University of Duisburg-Essen. All participants gave written informed consent. A detailed participant flow chart is provided in fig. S1. All studies were conducted in accordance with the Declaration of Helsinki and approved by the local ethics committees of the University Clinic Hamburg-Eppendorf (registration numbers PV3247 and PV3387) and the University Hospital Essen (registration number 13-5598-BO). Exclusion criteria were acute or chronic pain, any neurological or psychiatric condition, recent use of psychotropic or analgesic substances, and acute infections.

Day 1 and 2: Conditioning

All studies followed a similar schedule. At the beginning of day 1, written informed consent was obtained, and participants were introduced to the experimental procedures. Participants were told that the purpose of the study was to investigate mechanisms responsible for interindividual differences in the efficacy of "licensed analgesics routinely used in clinical care." Furthermore, exclusion criteria were examined, and participants were asked to complete a number of psychological questionnaires.

Participants were then introduced to the thermal stimulation and rating procedures according to a standardized protocol. Participants were instructed on how to rate the intensity of heat stimuli on a 101-point VAS, with end points marked as "no pain" and "unbearable pain." Subsequently, a temperature calibration procedure was performed to determine individual stimulation temperatures to ensure participant safety and to maximize statistical power by minimizing floor and ceiling effects. For temperature calibration, a pseudorandomized sequence of 16 noxious heat levels was applied to the volar surface of the left forearm. On the basis of the participant ratings of these stimuli, stimulation intensities corresponding to subjective pain intensity ratings of 20 and 80 VAS units were estimated by means of a regression analysis.

Next, a negative or positive treatment experience was induced by a conditioning procedure. To this end, a topical analgesic treatment was simulated. An inert, rectangular, moist, self-adhesive white cotton patch (a lidocaine-free "demonstration version" of Versatis Medicated Plaster; Grünenthal) was applied to a previously unstimulated location on the same forearm. Participants were informed that the patch contained an active analgesic drug that would be absorbed in a few minutes and exert an analgesic effect for about 1 hour. The site was marked with a colored marker pen to indicate its location. A waiting period of 20 min followed, during which the participants filled in further questionnaires, to "allow the medication to become effective." Subsequently, the patch was removed, and participants were asked to rate their analgesic treatment expectations on a VAS, with end points marked as "no pain relief" and "complete pain relief."

In the subsequent conditioning procedure, 20 heat stimuli [duration, 15 to 20 s; intertrial interval (ITI), 20 to 40 s] were applied to a "control site" on the volar surface of the left forearm. The applied heat temperature corresponded to a VAS rating of 80 for all groups, as determined in the calibration procedure (Fig. 1). Subsequently, another series of 20 heat stimuli was applied to the treated site. Again, for each stimulus, a VAS pain rating was obtained. Unbeknownst to the participants, the applied stimulus intensities differed between the control and the treated site, depending on the assignment to the positive or negative treatment experience groups (Fig. 1). Participants from positive groups received lowered stimulus intensity, corresponding to a VAS rating of 20 units on the treated site to mimic a strong analgesic effect of 60 VAS units, compared to the control site. In contrast, the negative groups received a stimulation intensity of 80 VAS units at both the control and the treatment site, aiming for no analgesic effect (0 VAS units). In all studies, the locations of control and treatment sites at the lower arm were pseudorandomized and balanced between groups. The treatment simulation and conditioning procedures described above were repeated on day 2 to reinforce positive and negative treatment experiences. In all cases, temperatures were applied as calibrated on day 1.

Day 3: Testing

On day 3, temperature calibration was repeated to ensure that individual temperature levels corresponded to VAS ratings of 50 and 80. Participants were then instructed that another analgesic with a different pharmacological profile would be administered. Groups without RoA change received the novel medication in topical form (ointment or transparent patch, depending on the substudy), whereas groups with RoA change received the novel medication in oral form (white pill or sublingual tablet, depending on the substudy). In all cases, the novel treatment differed visually from the previous treatment. After a waiting period of 20 min, participants were asked again to rate their treatment expectations on a VAS.

Subsequently, a series of 15 heat pain stimuli with an intensity of 80 VAS units was applied to the control site, followed by a series of 15 stimuli with an intensity of 50 VAS units applied to the treatment site. Therefore, all groups received the same calibrated temperature differences at the control and treatment sites, simulating a moderately analgesic effect of VAS on day 3.

Temperature stimulation and ratings

In all studies, noxious contact heat stimuli were applied on the middle volar left forearm using a PATHWAY system (Medoc) equipped with a 30 × 30–mm^2 ATS Thermode. A laptop with Presentation (Neurobehavioral Systems) was used to coordinate stimulation and experimental timing and to obtain a participant's ratings via an external keyboard using a second screen. Upcoming heat stimuli were cued by showing a red fixation cross on screen. After a variable anticipation phase (4 to 11 s), temperature was quickly (10°C/s) raised to the prespecified heat level and held constant for 15 to 20 s. Subsequently, the temperature was quickly ramped down (10°C/s) to baseline (35°C), and after a variable waiting period of 3 to 7 s, participants were asked to rate the preceding heat stimulus in terms of painfulness on the VAS. The next stimulus ensued after an ITI of 40 s.

Study-specific features

The six studies used the same experimental design except for the following differences: No ratings of treatment expectation were obtained in study 1. Furthermore, in studies 1 and 2, the order of placebo and control treatments was pseudorandomized (balanced across subjects). In all subsequent studies, the control condition was implemented before the treatment condition because the pain-alleviating effect of orally administered analgesics unfolds over the course of several hours, whereas our experimental sessions were limited to 3 hours. Control measurements for the groups with RoA change could therefore only be obtained before the intake of oral medication to maintain a plausible cover story. Notably, no significant effects of treatment sequence on rating differences between control and treatment sites were found in studies 1 and 2. In study 2, all testing procedures on day 3 were performed during functional magnetic resonance imaging (*10*), whereas in all other studies, participants were seated in a behavioral laboratory.

In studies 1 and 2, an inert white ointment (custom preparation by the pharmacy of the University Medical Center Hamburg-Eppendorf) was used as the novel topical treatment on day 3, whereas an inert, rectangular, self-adhesive, transparent skin patch (OPSITE FLEXIGRID Film, Smith and Nephew) was used in studies 4 to 6 for practical purposes (study 3 included only groups with RoA change).

In studies 3 and 5, an inert, white, lactose monohydrate pill (custom preparation by the pharmacy of the University Medical Center Hamburg-Eppendorf) was used as the novel oral treatment in the groups with RoA change. To allow for a plausible but shorter onset of the analgesic effect, a quickly dissolving lactose monohydrate tablet (P-Tabletten 7 mm, Winthrop Arzneimittel GmbH) was used and introduced as a "rapid sublingual preparation" in study 6.

In study 6, several stimulation parameters were shortened to reduce the duration (up to 3 hours) of sessions. The number of stimulus repetitions on conditioning days 1 and 2 was reduced from 20 to 15. The heat stimulus duration was reduced from 20 to 15 s, and the ITI was reduced from 40 to 20 s.

Although temperatures were individually calibrated, participant ratings often deviated from the targeted VAS ratings of 20 and 80 on conditioning days 1 and 2, resulting in between-subject differences in conditioning success. To prevent this deviation, we introduced a conditioning procedure with adaptive temperatures in study 6. A custom program (available on request) written for MATLAB 2015b (MathWorks), Psychtoolbox-3, and the external control software for PATHWAY systems (MEDOC) was used to subtly adapt temperatures over the course of a stimulus sequence. If a participant's responses deviated from the desired conditioning targets of 20 or 80 VAS units, the automated program increased or decreased the temperature for subsequent stimuli, while avoiding abrupt changes in heat levels. The adaption rate was 0.008°C/ΔVAS, calculated as the moving average difference from the target rating across three preceding ratings.

Statistical analysis

Analgesic treatment outcome was defined as the within-participant difference between the mean VAS pain ratings obtained at the control and treatment site (mean[$VAS_{control\ site}$] − mean[$VAS_{treatment\ site}$]) on day 3. We tested all the main and interaction effects of the factors treatment experience and RoA change on the treatment expectations and analgesic outcome in two separate GLM analyses. Paired *t* tests were used to explore day-to-day changes in treatment-related beliefs over the course of the experiment. Additionally, we tested whether treatment expectations were associated with outcomes by repeating the analysis for the analgesic outcome, adding treatment expectations as a continuous covariate.

The following considerations guided all statistical approaches:

(1) Treatment experience: Participants' mean ratings on days 1 and 2 varied considerably around the conditioning targets because of the limited accuracy of the temperature individualization procedure (see fig. S2, D and E). The conditioning procedure was therefore more effective in some participants than in others, potentially confounding the outcome. To account for differences in conditioning strength, treatment experience was not modeled as a simple two-level factor. Instead, we used the empirically observed mean within-participant difference between the VAS pain ratings obtained at the control and the treatment sites (mean[$VAS_{control}$] − mean[$VAS_{treatment}$]) across days 1 and 2. The resulting quasi-continuous variable was highly correlated with the original factor levels representing positive/negative groups ($r = 0.93$) but incorporated the additional variability in conditioning success.

(2) Study: Data from six experiments on treatment history were combined to maximize statistical power. Pooling data across studies and investigators can confound results and lead to paradoxical conclusions (*32*). Therefore, mean study differences were accounted for in all analyses by including the categorical factor "study."

(3) Temperature difference: Participants received different temperatures at the control and at the treatment sites on day 3. Because of the temperature individualization procedure, temperature differences between control and treatment sites varied between subjects. Imprecision in the temperature calibration procedure may confound pain rating differences. Thus, individual temperature differences between control and treatment locations ($temperature_{control}$ − $temperature_{treatment}$) on day 3 were modeled as a covariate for the analysis of analgesic outcomes. Notably, temperature differences could not causally affect treatment expectations obtained on the same day because expectations were obtained before heat testing.

Analyses were performed with R v3.2.4. The GLMs were built using the lm (stats package v3.2.4) function. The Anova function (car package v2.1-1) with type II sums of squares was used to test model terms in terms of variance explained. Therefore, all main effects are corrected for all other main effects but not for interactions; all one-way interactions are corrected for main effects and all other one-way interactions but not higher-order effects, etc. Type II sums of squares were chosen over the more common type III method because our study design was unbalanced, with missing cells (studies 1, 2, 3, and 4 included only two of four groups), which may complicate the interpretation of type III sums of squares (*33*). All continuous covariates were centered and standardized to the SD before entering the model. Pairwise comparisons were performed with lsmeans (v2.23). Classical η^2 values (SS_{factor}/SS_{total}) were computed using the lsr package v0.5. For data visualization, ggplot v2.1.0 was used. Nonparametric, bootstrapped CIs were obtained with R package boot v1.3-18 and its default BCa option. Data shown in Fig. 2 were corrected for mean study differences and temperature differences. For this purpose, residual values were extracted from a GLM containing the factors "study" and "temperature difference" and added to the intercept term. Supplementary figures depict raw data without correction. All statistical tests were performed at a two-sided significance level of $\alpha < 0.05$. The analyses for this study have been deposited at https://github.com/mzunhammer/TreatmentHistory2017.

SUPPLEMENTARY MATERIALS

www.sciencetranslationalmedicine.org/cgi/content/full/9/393/eaal2999/DC1

Fig. S1. Participant flowchart with reasons for exclusions.

Fig. S2. Treatment expectations, applied temperatures, and pain ratings by day and group.

Fig. S3. Treatment expectations on day 3 not correlated with treatment outcomes.

Table S1. Sample descriptions by substudy.

Table S2. Effects of treatment experience and RoA change on treatment expectations and treatment outcomes.

Table S3. Treatment expectations not predicting analgesic outcomes beyond treatment experience and RoA change.

Table S4. Age and gender not predicting analgesic outcomes beyond treatment experience and RoA change.

REFERENCES AND NOTES

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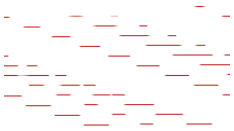

The effects of treatment failure generalize across different routes of drug administration
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Editor's Summary

No great expectations

The success of medical treatment, especially for subjectively evaluated conditions such as pain, is usually influenced by a patient's expectations. In particular, patients who have been exposed to unsuccessful treatment attempts in the past often do not respond as strongly to subsequent treatments. To assess whether a change in drug route (from topical patch to oral administration) can help with this, Zunhammer *et al*. evaluated the perception of pain in humans using a heat exposure model. The change in drug route improved the patients' conscious expectations of treatment success, but not the actual therapeutic efficacy, suggesting that a change of administration route is not sufficient to counter the effects of unsuccessful treatment exposure.