


ARTICLE

Savor the flavor: A randomized double-blind study assessing taste-enhanced placebo analgesia in healthy volunteers

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Abstract

Placebo effects substantially contribute to analgesic treatment outcomes and might be leveraged to enhance gold-standard treatments. The taste of oral medications has been proposed to boost placebo effects. Here, we aimed at estimating how far the taste of an oral medication enhances placebo analgesia. We conducted a randomized, double-blind, between-group, single-visit study, with pre-treatment baseline. Over the course of three substudies, 318 healthy volunteers (297 included) were tested in a clinical trial setting. Participants were subjected to experimental tonic cold water pain (cold pressor test) before and after receiving taste-neutral (water), or bitter (quinine), or sweet (saccharin), or no placebo drops. Pre- versus post-treatment changes in area under the pain rating curve, the main outcome, indicated that placebo treatment showed a small analgesic effect versus no treatment. Added taste induced placebo enhancement in the very small effect size range, but accounted for a substantial portion of the overall placebo effect. No noteworthy advantage of sweet over bitter placebo was observed. An exploration of heart rate (HR) recordings indicated that placebo treatments were associated with an increase in peak HR-response to cold water, but these were not associated with placebo analgesia at an individual level. Placebo treatments were associated with minimal side effects. These results indicate that added taste may be an easy-to-implement, cost-effective, and safe way to optimize treatment outcomes and that taste-neutral preparations may reduce placebo-related outcome variance in clinical trials. Further studies are needed to test if these findings can be translated into clinical scenarios.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Taste is a prominent characteristic of any oral medication and has been suggested to drive placebo effects, yet surprisingly few data are available to support this claim.

WHAT QUESTION DID THIS STUDY ADDRESS?

We performed a randomized, double-blind study in a total of 318 healthy volunteers to estimate: How much stronger is placebo analgesia induced by bitter- and sweet-flavored placebo drops versus neutral placebo and no treatment?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Overall, the study found that placebo effects were in the small to very small range, but bitter and sweet placebo drops were approximately 1.8 and 2.5 times more effective in reducing pain than neutral placebo. Placebo treatment caused minimal adverse effects, regardless of taste. Placebo treatments, especially the bitter placebo, enhanced the cardiac response to cold pressor stress.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Our results indicate that added taste may be an easy-to-implement, cost-effective, and safe way to optimize analgesic treatment outcomes, but confirmation in patients and clinical settings is needed. Further, these data suggest that using taste-neutral preparations may be key to reducing placebo-related outcome variance in clinical trials.

INTRODUCTION

Placebo effects are increasingly recognized as powerful modulators of health and treatment outcomes.¹ Placebo effects are not limited to inert placebo treatments but also contribute to active treatments²; this effect is particularly large for pain and depression where up to 70% of overall treatment outcomes may be attributed to placebo effects.¹ These discoveries call for a systematic exploitation of placebo effects in clinical care to enhance the efficacy of gold-standard treatments.³ Extensive research over past decades has linked placebo effects to expectancy, learning, and social cognition mechanisms,⁴ which are driven by various aspects of the treatment context, ranging from the information delivered along with a treatment,⁵ to features of the treatment itself, such as labeling,⁶ color,⁷ and even price.⁸

Taste is a prominent characteristic of any oral medication and has been suggested to modulate placebo effects.^{9,10} Studies in humans and rodents have indicated that pharmacologically induced immunosuppression can be re-evoked by presenting a conditioned taste, equivalent to a 'learned placebo effect'.¹¹ Yet, although placebo analgesia is the best studied form of the placebo effect,¹² surprisingly little is known about the impact of taste. This lack of knowledge is unfortunate, considering the dissatisfactory situation in many chronic pain settings, where established analgesics often show limited efficacy, for example, non-steroidal anti-inflammatory analgesics (NSAIDs) against chronic lower back pain.¹³ Adding flavor to oral medication could be a cost-effective and easy-to-implement way to utilize placebo effects in clinical care. Moreover, a better understanding of the gustatory component of placebo effects may be useful to improve the efficacy of clinical trials by minimizing placebo-related variability.^{14,15}

Here we performed a randomized, double-blind study in a total of 318 healthy volunteers to estimate the

analgesic effect of bitter and sweet flavor placebo treatment versus neutral placebo and no treatment. The experimental design is outlined in Figure 1. Pain was induced using the cold pressor task (CPT), an established experimental model of tonic pain.^{16,17} Continuous pain rating curves, compared pre- versus post-treatment, served as the primary outcome. Pain tolerance, adverse effects of the (placebo) treatment, and HR-responses were assessed as secondary outcomes. Further, the influence of

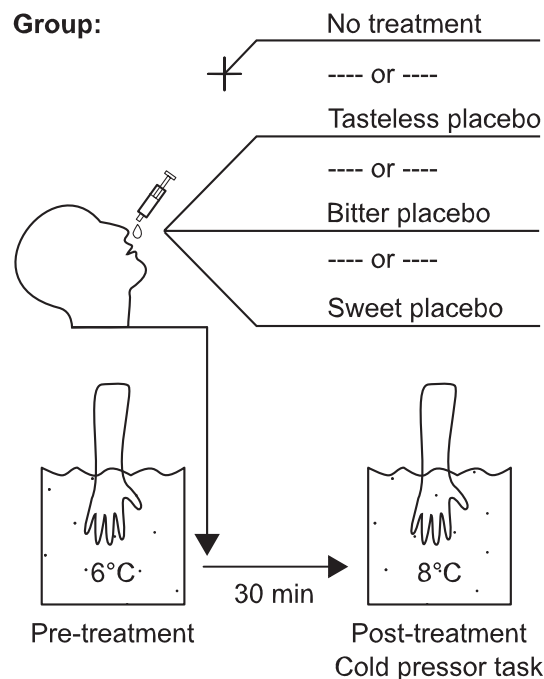


FIGURE 1 Experimental design. Across three substudies, participants were allocated to either receive no treatment, or tasteless placebo, or bitter placebo, or sweet placebo, after baseline testing. Water temperature was covertly increased by 2°C before post-treatment testing to simulate a weak analgesic treatment effect, as is typical for clinical settings.

participants' treatment expectation, subjective taste intensity, and/or taste valence ratings were assessed.

METHODS

Ethics and participants

The present study was conducted in accordance with the Declaration of Helsinki, and approved by the ethics committee of the Universitätsklinikum Essen (16-7163-BO and amendments). The study was registered in the German Clinical Trials Register (DRKS00011688), after the start of data collection. Healthy, young (age: 18–40 years) participants were recruited at the University of Duisburg-Essen by advertisement on bulletin boards. Participants were informed in writing and verbally, and signed consent was obtained before study inclusion and before any measures were undertaken. Participants were informed that the purpose of the study was to investigate “interaction effects between tried-and-tested analgesic drops and the individual genetic background”. Participants were not informed that the focus of the study was taste perception. The only explicit mention of medication taste was made after all testing was completed, when taste intensity and valence ratings were obtained. Predefined exclusion criteria were: history of neurological, psychiatric, or major internal disorders, Raynaud syndrome, injuries to the upper limbs, history of recurrent cramps or syncope, pregnancy, acute infections, alcohol consumption within the last 48 h, and use of analgesic or psychotropic substances within the last 2 weeks. All candidate participants were tested, regardless of exclusion criteria, as long as testing was deemed safe. The decision on study exclusion/inclusion was made after testing, before analysis, by M.Z. and U.B.; these measures were taken to reduce sampling bias. Participants received compensation of 50 €.

Study design

The present study encompasses three substudies. Each substudy followed the same experimental protocol and a randomized, double-blind, parallel group design, aiming for a 50:50 male:female ratio. Both the experimenters and the study participants were blind in respect to group allocation for the placebo-treated groups.

No blinding could be achieved for the no-treatment control group, as the knowledge of *not* being treated was essential. Substudy 1 was planned as a confirmatory study, with a target sample size of $n = 138$ and an allocation ratio of 1:1:1 to groups “no-treatment”, “taste-neutral placebo”, and “bitter placebo”. An interim analysis of Substudy 1 suggested insufficient statistical power, the

study was therefore extended by two further Substudies. Substudy 2 was conducted by author M.S. and was identical to Substudy 1 in terms of study design with a recruiting target of $n = 30$ additional participants. Substudy 3 was conducted by author M.S. Substudy 3 aimed at recruiting 150 eligible participants and a ‘sweet placebo’ condition was introduced to allow for a wider generalizability of the results in terms of taste.^{9,10} Participants were randomly assigned to one of four groups that either received no treatment, tasteless placebo, bitter placebo, or sweet placebo, with an allocation ratio of 1:1:1:3, respectively (for details see [Supplementary Methods](#)).

Placebo treatment

Oral drops were chosen as the mode of administration for placebo treatments. For the tasteless treatment group, placebo drops consisted of purified water. The bitter and sweet placebo groups received aqueous quinine (0.8 mM/L, 0.03 g quinine-dihydrochloride in 100 ml purified water) and saccharin (1.0 mM/L, 0.02 g Na-saccharin in 100 ml purified water) solutions, respectively. Doses were chosen according to pilot experiments, with the aim to elicit an intense taste that disappears within 30 min (see [Supplementary Methods](#), Figure S5). Drops were stored in sequentially numbered 1.0 ml plastic syringes at 4°C until administration by the experimenters. Experimenters applied 0.8 ml of placebo drops sublingually. Participants were unaware of the inert placebo nature of the treatment (blind placebo) and unaware that the purpose of the study was to investigate the effects of taste perception (for details see [Supplementary Methods](#)).

Testing schedule and auxiliary measures

The testing schedule was identical for all three substudies: After participants arrived at our laboratories at Essen University Hospital, informed consent was obtained, their current health status was examined, and potential exclusion criteria were recorded. Participants were introduced to the CPT and visual analog scale (VAS) rating procedures according to a standardized protocol. A first CPT was performed as a pre-treatment baseline. Then, oral placebo drops were applied in the treatment groups, while the non-treatment received no treatment. Subsequently, a 30-min waiting period was observed in all groups, during which participants were asked to complete questionnaires. The waiting period was implemented (a) to simulate the delay-of-onset of typical analgesic drugs, (b) to avoid confounding subsequent testing procedures with ongoing gustatory stimulation (e.g., through distraction), and (c) to

allow the skin to recover from pre-testing CPT. After the waiting period, expectations of treatment-induced pain relief were obtained in the treatment groups using a VAS shown on-screen. Subsequently, the post-treatment CPT was performed. After the CPT, participants in the treatment groups were asked to provide VAS ratings regarding the medication's (a) overall efficacy, (b) taste intensity, and (c) taste pleasantness. A blood sample was taken after testing to allow for genetic assessments in future studies. Lastly, participants were asked about treatment side effects and discharged after debriefing. Treatment-related side effects were queried systematically using a custom questionnaire (for details see [Supplementary Methods](#)).

Cold pressor test

CPT^{18,19} was performed at $6.0 \pm 0.2^\circ\text{C}$ pre-treatment and at $8.0 \pm 0.2^\circ\text{C}$ post-treatment CPT. Water temperature was covertly increased by 2°C before post-treatment testing to simulate a weak analgesic treatment effect, as is typical for clinical settings. In the CPT, participants submerged their non-dominant hand into cold water for as long as tolerable, or a safety maximum of 180 s, while continuously rating pain intensity on a 101-point VAS (VAS endpoints: "0: no pain", "100: unbearable pain"), using a mechanical sliding lever. Participants could terminate testing at any time. Continuous heart rate (HR) recordings were obtained from the ring finger of the dominant hand using a standard bedside monitor (Infinity Delta) equipped with a pulse spectrophotometer. Starting and termination times of CPT were logged by the experiments via button press (for details see [Supplementary Methods](#)).

Statistical analysis

Individual pain sensitivity was calculated based on the continuous pain rating curves obtained in CPT (Figure S1), the primary outcome metric was area-under-the-pain-curve (AUPC) according to Koltzenburg et al. and Jones et al.^{16,20} AUPC is an established summary metric for continuous CPT pain ratings and has been shown to be sensitive for detecting opioid analgesia.^{16,21,22} A higher normalized AUPC indicates higher individual pain sensitivity: an AUPC of 0% denotes a constant VAS pain rating of 0, whereas an AUPC of 100% denotes the immediate termination of testing due to pain intolerance or, equivalently, a constant VAS rating of 100 for 180 s. CPT-tolerance time, that is, the period that participants endured the CPT before retracting their hand from the water bath, was explored as a

secondary outcome in participants terminating testing early, and $\text{AUPC}_{\text{mean}}$ was explored as a secondary outcome in non-terminators.

Further, we assessed adverse effects attributed to the (placebo) treatment and temporary CPT-induced increases in HR as secondary outcomes. The HR-response during CPT was calculated as the peak HR (HR_{max}) observed during the CPT period, minus a 15-s-long pre-CPT HR-baseline, and assessed as a secondary outcome measure.

Robust, non-parametric, general linear model (GLM) analysis was performed for each outcome to estimate the effects of factor-of-interest *group* (levels: no treatment, tasteless placebo, bitter placebo, sweet placebo) on post-treatment values. Pre-treatment values were included as a covariate, to account for inter-individual baseline differences, as recommended in Egbevale et al.²³ The fixed factor *study* (levels: Substudy 1, Substudy 2, Substudy 3) was used to account for potential substudy differences (see Table S2).

GLMs were assessed in terms of variance explained (ANCOVA, *F*-test) and followed-up by paired contrasts (*t*-tests on parameter estimates). Partial η^2 are provided for all *F*-tests and β -estimates for all *t*-tests. Cohen's *d* was calculated as the mean group difference between intra-individual pre-to-post-treatment changes, divided by the SD of individual changes. To facilitate comparisons with clinical results, numbers needed to treat were calculated for the primary outcome, whereas treatment responders were defined as the fraction of participants experiencing a pain reduction of $>30\%$, relative to pre-treatment baseline.²⁴ Parameter estimates are provided with bootstrapped 95% confidence intervals (95% CI). All analyses were interpreted from a parameter estimation perspective, focusing on effect sizes not *p* values²⁵ (for details see [Supplementary Methods](#)).

All analyses were repeated in an intention-to-treat fashion including *all* tested participants (regardless of exclusion criteria) to allow for detecting deliberate selection bias. CPT HR-response, treatment expectation ratings, taste intensity ratings, and taste valence ratings were explored for associations with %AUPC to aid the interpretation of results. The data and analysis code are available online at https://github.com/mzunhammer/analysis_placebo_taste.

Ethics approval

The present study was conducted in accordance with the Declaration of Helsinki, and approved by the ethics committee of the Universitätsklinikum Essen (16-7163-BO and amendments).

RESULTS

We recruited, allocated, and tested 318 participants across three substudies; 21 participants (6%) were excluded from the main analysis based on predefined exclusion criteria, yielding a sample of 297 (Table 1, Table S2, Supplementary Methods).

Primary outcome: pain ratings in the CPT

Mean pain rating curves and changes in AUPC from pre- to post-treatment are shown in Figure 2 (also see Table S2). The factor of interest *group* explained ~6% of residual variance in post-treatment AUPC, which is considered a small-to-moderate effect in statistical terms²⁶ (Table 2). As expected, the covariate *pre-treatment AUPC* was the best predictor of post-treatment values, explaining most of the variance (86%) in post-treatment AUPC (Table 2), justifying its use as a baseline control. The factor *substudy* explained little variance (1%) indicating that mean substudy differences played a minor role in treatment-related changes.

Contrasts indicated that placebo treatment (pooled: neutral, bitter, sweet) was superior to no treatment, reducing AUPC by an estimated -5.31%, 95% CI [-8.19, -2.78] ($\beta = -0.20$, 95% CI [-0.30, -0.11], $t(292) = -3.87$, $p < 0.0001$, Cohen's $d = 0.37$); 6.9 participants needed to be treated with *any* placebo to achieve an additional responder (defined as -30% pain reduction from baseline) over no treatment. This is considered a small effect in both clinical²⁴ and statistical²⁶ terms. Individually, all three placebo groups showed a small benefit (standardized effect size: ~0.2 standard deviations²⁶) over the no-treatment group (see Table 2).

Flavored placebo groups (pooled) showed an additional AUPC reduction by -2.57%, 95% CI [-5.35, 0.26] ($\beta = -0.09$, 95% CI [-0.19, 0.01], $t(291) = -1.80$, $p = 0.125$, Cohen's $d = 0.13$) over the tasteless placebo group; 7.2 participants needed to be treated with flavored placebo to achieve an additional responder. This is considered a very small absolute effect in both clinical²⁴ and statistical²⁶ terms. Nevertheless, the taste-enhancement effect amounted to +72% (95% CI [+151%, -7.3%]) of the observed placebo effect in the taste-neutral group or, equivalently, a boost-factor of 1.72. Also independently, bitter and sweet placebo treatment groups showed an additional benefit versus neutral placebo (standardized effect size: ~0.1 standard deviations, Table 2), with sweet placebo showing a marginal advantage over bitter placebo (Table 2).

Auxiliary analyses were performed to corroborate these findings (also see Supplementary Results, Figure S2): Of note, effect size estimates and statistical test results were confirmed, when repeating the analysis with all participants tested, including those fulfilling the predefined exclusion criteria (Table S3), which largely excludes that deliberate selection bias affected analysis. Moreover, directions of effect and effect sizes were essentially confirmed, when separately analyzing maximum pain tolerance time in the subgroup of participants terminating testing early (Table S4) and average pain rating in the subgroup that did not terminate testing (Table S5), instead of using AUPC as a summary measure.

Secondary outcome II: adverse effects

Levels of adverse effects were very low across the sample (Table S8). Most participants ($n = 191$, 64% of the per-protocol sample) did not report any placebo-related side effects and no

TABLE 1 Sample descriptives pooled across substudies

Group	No treatment	Taste-neutral placebo	Bitter placebo	Sweet placebo	Total
Randomized, n	81	81	81	75	318
Excluded, n^a	10	6	2	3	21
Per-protocol sample, n^b	71	75	79	72	297
HR recordings, n^c	68	71	74	67	280
Sex (% male), %	49	45	51	60	51
Age, mean (SD)	24.3 (2.7)	24.4 (3.4)	24.6 (3.4)	24.4 (3.2)	24.5 (3.2)
Handedness (% right), %	92	91	97	96	94

Abbreviations: CPT, cold pressor test; HR, heart rate; SD, standard deviation.

^aReasons for exclusion were: previous participation in similar studies ($n = 5$), alcohol consumption on the day before testing ($n = 4$), lack of pain response at CPT-baseline ($n = 3$), dizziness/hypotension in response to CPT-testing ($n = 2$), psychiatric diagnoses ($n = 2$), surgery within the last 6 months, or use of analgesic medication within the last week ($n = 3$), an endocrine condition ($n = 1$), technical failure during testing ($n = 1$).

^bAn additional intention-to-treat analysis was performed with all available data.

^cNumber of participants where both pre- and post-treatment HR recordings could be analyzed. Reasons for additional exclusion compared to the per-protocol sample were: recording failure ($n = 16$) and extreme values ($n = 1$).

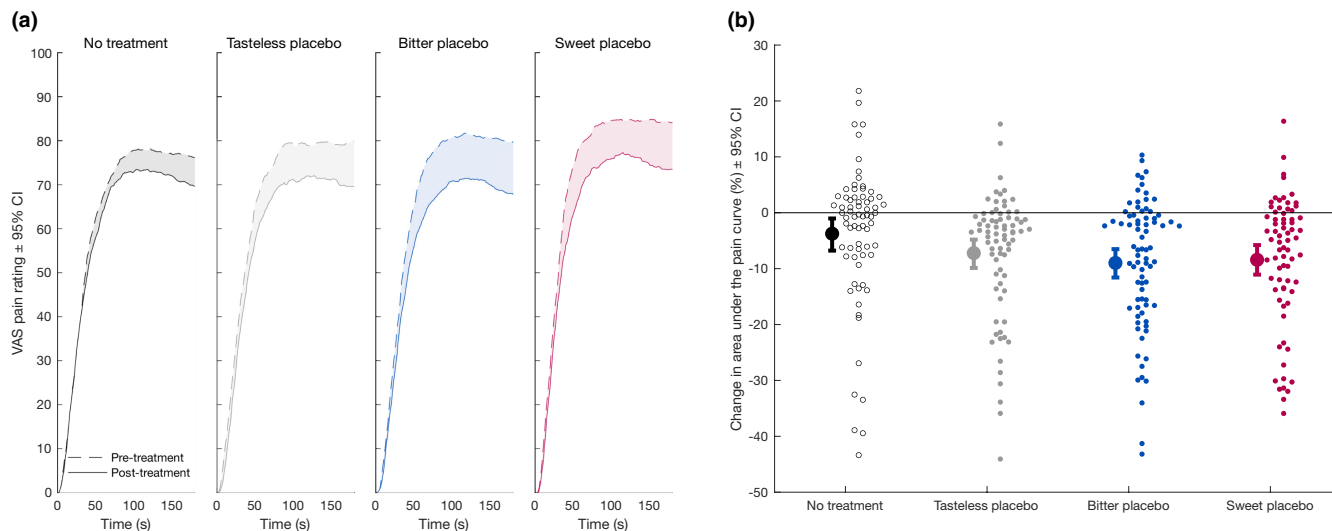


FIGURE 2 Analgesic effects of placebo treatment on (a) continuous pain ratings and (b) area under the pain rating curve (AUPC). (a) Mean pain rating curves obtained during cold pressor test (CPT) for pre-treatment at 6°C (dashed lines) and post-treatment at 8°C (solid lines) timepoints. Ratings of participants terminating testing before the maximum of 180s were carried forward with a pain rating of 100. Differences in pain rating curves over time are highlighted as an area and correspond to the means in (b). (b) Means \pm bootstrapped 95% CIs (BCa) of area under the pain rating curve in percentages, shown next to individual data points ($n = 297$). Negative values indicate that post-treatment pain ratings were lower than pre-treatment ratings. Abbreviations: CI, confidence interval; VAS, visual analog scale.

TABLE 2 General linear model results of percentage area under the pain curve and contrasts of factor group

GLM results of %AUPC				
Model term	Df ₁	F	Partial eta ²	p*
Pre-treatment %AUPC	1	1769	0.859	<0.0001
Study	2	1.68	0.011	0.189
Group	3	5.86	0.057	0.0005
GLM contrasts of factor group, for %AUPC				
Model term	B [95% CI]**	Beta [95% CI]**	t	p*
Neutral placebo > no treatment	-3.55 [-7.06, -0.75]	-0.13 [-0.26, -0.02]	-2.16	0.069
Bitter placebo > no treatment	-5.77 [-9.39, -2.77]	-0.21 [-0.35, -0.11]	-3.54	0.003
Sweet placebo > no treatment	-6.76 [-10.9, -3.62]	-0.25 [-0.40, -0.13]	-3.53	0.0004
Bitter placebo > neutral placebo	-2.22 [-5.34, 0.96]	-0.08 [-0.20, 0.04]	-1.38	0.246
Sweet placebo > neutral placebo	-3.21 [-6.83, 0.03]	-0.12 [-0.25, 0.00]	-1.68	0.095
Sweet placebo > bitter placebo	-0.99 [-4.80, 2.32]	-0.04 [-0.18, 0.08]	-0.52	0.612

Note: Per-protocol sample $n = 297$. *Values of p are based on random (Monte Carlo) permutation testing. **95% CIs based on bootstrapping (asymmetric, BCa method). B denotes unstandardized model coefficients (unit: %AUPC), beta values show standardized model coefficients (unit: standard deviations). $df_2 = 290$, Adjusted $R^2 = 0.866$.

Abbreviations: AUPC, area under the pain curve; CI, confidence interval; GLM, general linear model; HR, heart rate.

single rating exceeded “moderate” severity. Two participants reported dizziness and/or showed signs of hypotension in response to CPT-testing after completing the experimental session. The most frequent side effect was “drowsiness” ($n = 65$), followed by “feeling hot” ($n = 28$) and “palpitations” ($n = 24$). Average side effect scores were very low (0.8 ± 1.2 units of 78 units possible) and there were no detectable differences in side effects scores between placebo groups ($F[2, 218] = 0.15$, $p = 0.859$, partial eta² = 0.0007), even when only considering

participants that showed any side effects ($F[2, 89] = 0.08$, $p = 0.925$, partial eta² = 0.0009).

Secondary outcome III: HR

CPT typically induces a temporary spike in HR.^{27,28} These increases in HR are a compensatory cardiac response²⁹ to the cold stressor, and have been suggested to reflect

autonomic nervous system responsivity, that is, sympathetic activation and parasympathetic deactivation.^{28,30,31}

Here, we estimated treatment group effects on the peak CPT HR-response as a secondary outcome measure that may also shed light on the mechanisms and physiological effects of placebo treatment. Valid HR-recordings were available for 280 of the 297 participants in the per-protocol sample (Table 1); 17 participants could not be analyzed due to missing or invalid recordings. Single-participant HR-curves during CPT are provided in Figure S3, and descriptive results are provided in Table S6.

Mean continuous HR-curves during CPT and CPT HR-peak amplitudes are shown in Figure 3. ANCOVA indicated that treatment group explained ~7% of residual variance in post-treatment AUPC, which is considered a small-to-moderate effect in statistical terms (Table 3). In the no-treatment group, peak HR responses to the second CPT were clearly reduced compared to the first CPT (Figure 3), which is expected as the second CPT was a weaker stressor (water bath was +2°C warmer) and since HR-responses to CPT are known to attenuate with repeated exposure.²⁷ Contrarily, placebo treatments increased peak CPT HR-response over no treatment by +2.92 beats per minute (bpm) (95% CI [0.91, 4.91], $\beta = 0.34$, 95% CI [0.10, 0.56], $t(275) = 2.78$, $p = 0.006$). In particular, flavored placebo groups showed increased CPT HR-responses compared to neutral placebo (+3.23 bpm, 95% CI [1.09, 5.17], $\beta = 0.38$, 95% CI [0.16, 0.57], $t(274) = 2.94$, $p = 0.005$), with a pronounced effect in the bitter placebo

group (Table 3). These results indicate that flavored placebo treatments, particularly bitter treatment, increase HR-responses to the cold water challenge relative to neutral-tasting placebos. Several auxiliary analyses were performed to corroborate these findings: In short, no pre- or post-treatment group differences in baseline HR were detected and results were replicated when repeating the analysis with all participants tested (see Supplementary Results, Table S7). Of note, there was no appreciable relationship between pre-treatment peak CPT HR-response and AUPC (see Figure S4), suggesting that peak CPT HR-response is not a surrogate marker of pain, replicating previous findings.^{32,33}

Intervention checks and auxiliary analyses

To aid the interpretation of potential placebo and taste effects, we explored participant ratings of treatment expectations, subjective taste intensity, and taste valence. Expectations of analgesia were moderate on average (41.9 ± 20.2 , Table S8) and the factor group did not explain sizeable amounts of variance ($F[2, 221] = 0.304$, $p = 0.738$, partial $\eta^2 = 0.0014$, corrected for fixed sub-study effects). Taste intensity ratings strongly differed between levels of factor *group* ($F[2, 221] = 65.6$, $p < 0.001$, $\eta^2 = 0.238$), with higher taste intensity ratings in the bitter ($b = +30.4$, 95% CI [24.5, 36.3], $\beta = +1.21$, 95% CI [0.98, 1.45], $t = 10.1$, $p < 0.001$) and sweet ($b = +9.1$, 95%

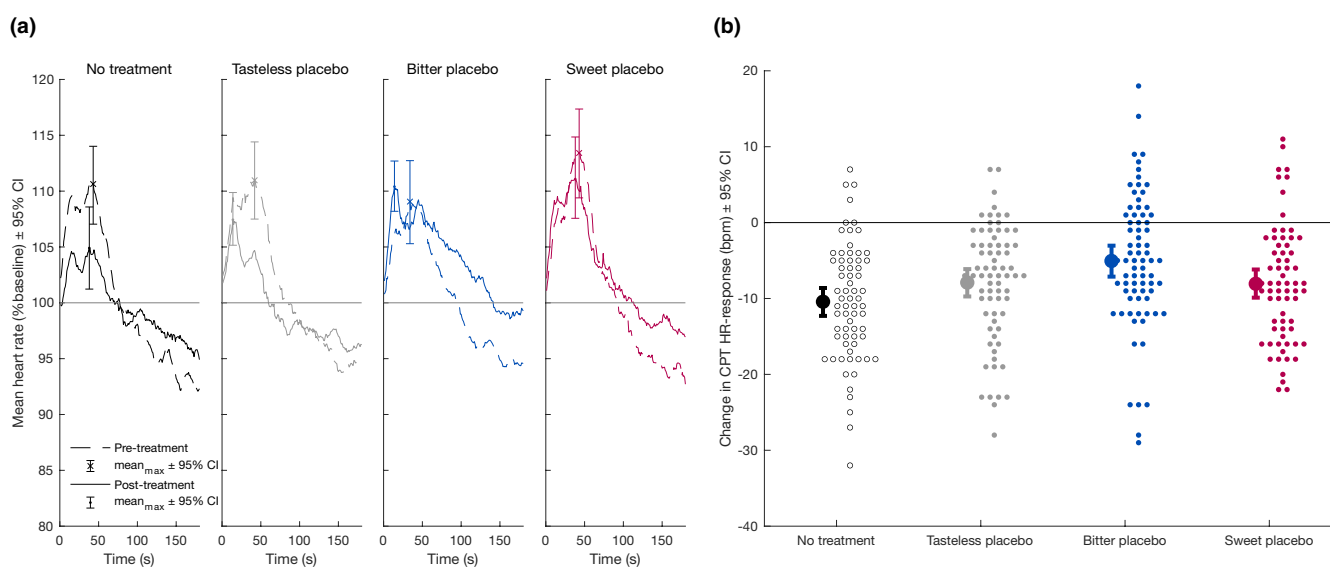


FIGURE 3 Effects of placebo treatment on (a) continuous heart rate (HR) recordings during the cold pressor test (CPT) and (b) change in CPT HR-response (pre- vs. post-treatment). (a) Mean HR-curves obtained during CPT for pre-treatment at 6°C (dashed lines) and post-treatment at 8°C (solid lines) timepoints. Maxima of mean HR-curve are highlighted \pm bootstrapped 95% CIs (BCa). (b) Means \pm bootstrapped 95% CIs (BCa) of change in CPT HR-response from pre- to post-treatment timepoints, shown next to individual data points ($n = 280$). Negative values indicate that the post-treatment HR-response (maximum HR-peak during CPT) was smaller than pre-treatment response. Abbreviations: bpm, beats per minute; CI, confidence interval.

TABLE 3 General linear model results of cold pressor test heart rate-response and contrasts of factor group

GLM results of CPT HR-response				
Model term	Df ₁	F	Partial eta ²	p*
Pre-treatment %AUPC	1	58.0	0.175	<0.0001
Study	2	1.31	0.010	0.270
Group	3	6.41	0.066	0.00018
GLM contrasts of factor group, for CPT HR-response				
Model term	B [95% CI]**	Beta [95% CI]**	t	p*
Neutral placebo > no treatment	0.92 [-1.43, 3.37]	0.11 [-0.17, 0.4]	0.74	0.069
Bitter placebo > no treatment	4.99 [2.57, 7.53]	0.58 [0.3, 0.89]	4.04	0.0004
Sweet placebo > no treatment	2.7 [-0.18, 5.31]	0.32 [-0.03, 0.62]	1.88	0.246
Bitter placebo > neutral placebo	4.07 [1.73, 6.54]	0.47 [0.2, 0.75]	3.34	0.095
Sweet placebo > neutral placebo	1.78 [-1.16, 4.55]	0.21 [-0.13, 0.54]	1.24	0.612
Sweet placebo > bitter placebo	-2.29 [-5.67, 0.79]	-0.27 [-0.65, 0.09]	-1.58	0.612

Note: Per-protocol sample (*w* valid HR recordings) *n* = 280. *Values of *p* are based on random (Monte Carlo) permutation testing. **95% CIs based on bootstrapping (asymmetric, BCa method). B denotes unstandardized model coefficients (unit: beats per minute), beta values show standardized model coefficients (units: standard deviations). df₂ = 273, Adjusted R² = 0.205.

Abbreviations: AUPC, area under the pain curve; CI, confidence interval; CPT, cold pressor test; GLM, general linear model; HR, heart rate.

CI [1.7, 16.5], $\beta = +0.36$, 95% CI [0.07, 0.66], $t = 2.41$, $p = 0.017$), compared to the tasteless placebo group (7.6 ± 10.3 , Table S8). Of note, taste intensity ratings in the bitter group were elevated compared to the sweet group ($b = +21.2$, 95% CI [13.8, 28.7], $\beta = +0.85$, 95% CI [0.55, 1.15], $t = 5.58$, $p < 0.001$), indicating that sweet and bitter conditions were not fully equivalent in terms of recalled taste intensity, despite two pilot studies that aimed at balancing taste intensity (Figure S5). Retrospective taste valence ratings also strongly differed between groups ($F[2, 221] = 33.7$, $p < 0.001$, $\eta^2 = 0.152$). On average, the taste of placebo medication was recalled as neutral in the tasteless group (mean = -3.6 ± 9.2 , Table S8), as moderately unpleasant in the bitter group ($b = -9.91$, 95% CI [-14.3, -5.50], $\beta = -0.52$, 95% CI [-0.74, -0.29], $t = -4.40$, $p < 0.001$), and as moderately pleasant in the sweet group ($b = +13.3$, 95% CI [7.70, 18.8], $\beta = +0.69$, 95% CI [0.40, 0.98], $t = 4.67$, $p < 0.001$). Taken together, these results indicate that our three placebo interventions successfully induced beliefs of pain relief and successfully evoked gustatory experiences that differed in terms of pleasantness. An exploratory analysis of potential associations of AUPC with ratings of treatment expectations, taste intensity, or taste valence merely indicated weak relationships (Table S9).

DISCUSSION

Here, we assessed the effects of flavored versus unflavored placebo treatments against experimental pain in healthy

volunteers and found that (a) bitter and sweet placebo drops were 1.8 and 2.5 times more effective in reducing pain than neutral placebo, (b) placebo treatment caused minimal adverse effects regardless of taste, and (c) placebo treatments, especially the bitter placebo, enhanced the cardiac response to cold pressor stress.

Our results indicate that the analgesic efficacy of oral placebo medication can be enhanced by adding flavor and, more generally, that sensory experiences that accompany medical treatments can enhance placebo effects. The estimated additional benefit of taste-enhanced placebo treatment (as compared to neutral placebo) was very small (-2.57% AUPC, Cohens $d = 0.13$), and therefore limited when compared to the effect sizes typically reported in CPT experiments for opioids,^{16,20} ketamine,³⁴ and pregabalin,³⁴ yet comparable to the effect sizes reported for several NSAIDs.³⁴ Contrary to tried-and-tested drugs, taste-enhanced placebo drops may provide additional analgesic effects with minimal risk, side effects, or costs. Considering the dissatisfactory situation in many chronic pain settings, where established analgesics often show limited efficacy³⁵ (e.g., see NSAIDs against chronic low back pain¹³), our present results highlight a potential 'low hanging fruit' for additional patient benefit. Further trials are needed to test whether our findings can be translated to verum analgesics, and whether clinical populations can benefit from flavored gold-standard verum analgesics. Moreover, taste enhancement may be of relevance for open-label placebo treatments, which are increasingly recognized as therapeutically relevant in pain disorders.³⁶⁻³⁸ Based on previous findings³⁹ we

are optimistic that the reported effect may be even larger in patients.

The overall placebo effect on pain ratings observed in this study was small ($d = 0.37$), while previous experimental placebo studies typically report large effect sizes of $d = 1.0$ (standard deviations).⁴⁰ This difference can be explained by the fact that most experimental placebo studies rely on within-subject designs⁴⁰ and include conditioning procedures to enhance the magnitude and sustainability of placebo analgesia.⁴¹ Here, we deliberately chose a between-subject design and induced placebo analgesia through verbal information only. This decision was based on several reasons. First, within-subject comparisons of treatment conditions may affect gustatory perception and introduce biases in judgment and decision-making or ‘demand characteristics’ as participants are able to directly compare treatments.⁴² Second, we wanted to use a placebo setting that is ready-to-implement into clinical routine. While the experience of treatment efficacy, as induced in conditioning protocols, can boost treatment responses,⁴³ the translation of such a strategy into clinical settings can be difficult, given that often no efficient treatment is available to induce a positive treatment experience. Third, we wanted to keep our study comparable to clinical trial settings, where participants are typically naïve to a novel treatment. These design choices distinguishes our study from earlier studies in the field of placebo research that, for example, achieved immunomodulation via taste stimuli.^{11,44}

Besides its use as a model of experimental pain, the CPT is an established stress test for cardiovascular and autonomic nervous system function.⁴⁵ In the first minute after CPT onset, HR and biomarkers of sympathetic nervous system activity typically increase and biomarkers of parasympathetic nervous system activity decrease, returning to, or below, baseline thereafter.^{28,30,31,45,46} Here, we found that the peak HR-response to CPT was affected by placebo treatment and placebo flavor. The no-treatment group showed diminished HR-responses in the second CPT session, while placebo treatment groups, especially the bitter treatment group, showed equally high HR-response in both the pre- and post-treatment CPT sessions (Figure 3). No appreciable relationship between individual HR-responses and individual placebo analgesia was found, which indicates that the two effects may be independent. These results are remarkable for two reasons. First, to date only a few studies could demonstrate placebo effects on physiological, cardiac outcome parameters in a sizeable sample.^{12,47} Second, our findings link placebo treatment, but not necessarily placebo analgesia, to increased cardiac autonomic nervous system responses under cold pressor

stress. The detailed mechanisms and causality of this observed placebo effect on HR-responses are unclear to date. However, we speculate that the observed autonomic cardiac response may reflect a general defensive and/or self-regulatory response to placebo treatment.

Several additional findings from our study could provide further insights into the underlying mechanisms of these taste-enhanced placebo effects: Although participants in all placebo groups reported sizeable expectations of pain relief, expectations showed no sizeable difference between placebo taste groups. Further, in our study individual treatment expectations showed no association with placebo analgesia. This may be explained by the overall very small effect sizes obtained. Alternatively, these findings may indicate that the taste-induced placebo analgesia is insufficiently explained by conscious treatment-related beliefs and hence related to non-conscious mechanisms.^{48,49} Moreover, participants’ recall of subjective pleasantness/unpleasantness of treatment taste showed no sizeable relationship with pain ratings. These results suggest that taste-related placebo effects in adults may not primarily be driven by the hedonic qualities of the treatment, distinguishing tasted-enhanced placebo effects in adults from the sweets-induced analgesia observed in neonates.⁵⁰ In this context we still would recommend using pleasant, rather than unpleasant, flavors in future studies, as the taste of oral medication could impact treatment outcomes beyond placebo effects (e.g., reduce adherence to the treatment regimen and thus treatment efficacy).

In summary, our results indicate the taste of a medication is a relevant contextual treatment factor that contributes to placebo analgesia. Our findings have to be interpreted in the light of several limitations. As the study sample size was extended in two steps (Substudies 2 and 3) the present study must be considered exploratory, not confirmatory, according to the null-hypothesis significance testing paradigm. Further, data were obtained in healthy volunteers, in a controlled experimental setting, using inert placebo treatments, and experimental pain stimulation. Moreover, our present study was limited to two moderately intense taste qualities, namely bitter and sweet in comparison to tasteless placebo drops. Therefore, it is unclear whether these results translate to actual pain patients, clinical settings, verum analgesics, or other complex flavors. Future trials in patients and clinical settings, covering a wider range of taste dimensions, are necessary to confirm whether our findings can translate to verum analgesics and patient benefit in real-world settings.

AUTHOR CONTRIBUTIONS

M.Z. designed the research, analyzed the data, and wrote the manuscript. G.G. and M.S. performed the research.

B.A.S. designed the research and contributed new reagents. U.B. wrote the manuscript and designed the research.

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CONFLICT OF INTEREST

M.Z. is currently employed by Takeda Pharmaceutical. The company was not associated with the present study in any way. The authors declared no competing interests for this work.

DATA AVAILABILITY STATEMENT

The underlying data and analysis are available online at https://github.com/mzunhammer/analysis_placebo_taste. The pre-review manuscript is available as a pre-print at <https://www.medrxiv.org/content/10.1101/2021.08.16.21262058v1>.

INFORMED CONSENT

Informed consent was obtained from every participant.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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