Research Paper

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Side effects can enhance treatment response through expectancy effects: an experimental analgesic randomized controlled trial

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Abstract

In randomized controlled trials, medication side effects may lead to beliefs that one is receiving the active intervention and enhance active treatment responses, thereby increasing drug–placebo differences. We tested these hypotheses with an experimental double-blind randomized controlled trial of a nonsteroidal anti-inflammatory drug with and without the addition of atropine to induce side effects. One hundred healthy volunteers were told they would be randomized to either combined analgesics that might produce dry mouth or inert placebos. In reality, they were randomized double blind, double-dummy to 1 of the 4 conditions: (1) 100 mg diclofenac + 1.2 mg atropine, (2) placebo + 1.2 mg atropine, (3) 100 mg diclofenac + placebo, or (4) placebo + placebo, and tested with heat-induced pain. Groups did not differ significantly in demographics, temperature producing moderate pain, state anxiety, or depression. Analgesia was observed in all groups; there was a significant interaction between diclofenac and atropine, without main effects. Diclofenac alone was not better than double-placebo. The addition of atropine increased pain relief more than 3-fold among participants given diclofenac ($d = 0.77$), but did not enhance the response to placebo ($d = 0.09$). A chain of mediation analysis demonstrated that the addition of atropine increased dry mouth symptoms, which increased beliefs that one had received the active medication, which, in turn, increased analgesia. In addition to this indirect effect of atropine on analgesia (via dry mouth and beliefs), analyses suggest that among those who received diclofenac, atropine directly increased analgesia. This possible synergistic effect between diclofenac and atropine might warrant future research.

Keywords: Expectancy, Unblinding, Placebo analgesia, Induced side effects, RCT model, NSAID

1. Introduction

The design of placebo-controlled randomized clinical trials (RCTs) implicitly assumes that drug and placebo effects are additive, such that the drug effect is the difference between the response to the drug and the response to the placebo. Data from studies contrasting open and hidden administration of medication as well as research showing that the probability of receiving a placebo affects the response to the active drug support this assumption.[4,11,17] For example, according to meta-analyses, open-label or active comparator trials produce larger drug responses than placebo-controlled trials,[49,54] and drug responses decrease as the number of RCT arms increases.[40,53] Studies assessing the relationship between side effects and drug–placebo differences provide additional support for the additivity hypothesis. Side effects might lead participants in clinical trials to break blind and realize that they have been given the active medication, which, in turn, might enhance their response.[43,52] In fact, correct guesses of treatment assignment have been linked to greater drug–placebo differences,[7,34] and the perception of side effects has been tied to treatment outcome.[36,52] Furthermore, clinical trials of treatments for depression and dental pain indicate that patients' beliefs about treatment assignment have stronger associations with clinical outcomes than the treatment that was actually received.[8,15,60]

Although some data support the additivity assumption, other studies point towards more complex interactions between drug and placebo effects.[30] For example, a large asthma study of 601 patients found that optimistic messages increased the effects of a placebo treatment, but not of the active medication.[65] Meta-analyses have found larger increases in responses to placebo than to active drug over time (ie, year of publication), with consequent diminution of drug–placebo differences,[45,58,63] contradicting earlier findings of parallel increases in drug and placebo responses.[62] Complicating the issue even further, one study reported additive effects of caffeine and information about the drug on one outcome (alertness), but an interaction on another outcome (tension).[28] Thus, the degree to which placebo and drug effects are additive remains unresolved.

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Determining whether drug and placebo effects are additive or interactive would have important implications for establishing the efficacy of various treatments. Additivity would support the implicit logic of the current RCT methodology, but would also open the possibility that treatment effects may be overestimated for drugs with noticeable side effects.[52] Conversely, it has been hypothesized that large placebo responses could be masking true drug effects, rendering it increasingly difficult to establish the efficacy of new drugs.[44,48,58]

In this experimental RCT, we evaluated whether drug and placebo effects are additive or interactive in the treatment of pain by testing the analgesic effects of diclofenac, a nonsteroidal anti-inflammatory drug (NSAID), with and without an induced side effect (dry mouth) produced by the addition of atropine (**Fig. 1**). We also hypothesized a mediational chain in which atropine would lead to dry mouth; dry mouth would foster the belief that one had received the active medication, and this belief would, in turn, enhance the analgesic response.

2. Methods

2.1. Sample

Participants recruited from the general population in Boston, Massachusetts were screened to be healthy. Exclusion criteria were chronic intake of medication except birth control, chronic pain, a psychiatric condition, or any condition (eg, gastritis, pregnancy, and high blood pressure) with increased risk for NSAIDs or atropine. Of the 101 participants invited to the clinical test center, one woman presented with exclusion criteria (hypertension) (see Consort diagram, available online at http://links.lww.com/PAIN/A391). One hundred participants (51 women, age range 18-38 years old, mean age = 23.82 ± 4.56) were randomized to 1 of the 4 conditions. We calculated a priori that 25 participants per cell would be sufficient to detect an effect size comparable with that obtained in a previous study of placebo analgesia ($d = 0.30$)[61] with 80% power.

2.2. Procedure

Healthy adults were invited to participate in "a research study on a combination of Food And Drug Administration–approved non-opioid pain medication that will be tested against placebo." During the written consent procedure, participants received full information about the side effects of diclofenac and atropine. The information sheet stated "Possible side effects of atropine and diclofenac include: Dry mouth; Hot, red, dry skin; Blurry vision (issues with visual accommodation); Slower or faster heartbeat; High blood pressure; Stomach ulcer and bleeding; Skin rash." This was read out to the participants, and commented: "Most of these side effects are unlikely to occur in a young, healthy person. However, most participants do experience some degree of dry mouth. This resolves within 2 to 4 hours of taking the drug, and is in general well tolerated." Participants were told they would be randomized to either combined analgesics that might produce dry mouth or inert placebos. In fact, participants were randomized double blind, double-dummy to 1 of the 4 conditions: (1) 100 mg diclofenac + 1.2 mg atropine, (2) placebo + 1.2 mg atropine, (3) 100 mg diclofenac + placebo, or (4) placebo + placebo and tested with induced heat pain. Such a balanced placebo design allows one to test drug and expectancy effects as well as their interaction.[20] Diclofenac is an NSAID. Atropine, an antimuscarinic given to induce dry mouth, was presented deceptively as an analgesic; participants were fully debriefed at the conclusion of the session.

Testing took place at the Center for Clinical Investigations at Brigham and Women's Hospital between June and November 2014. Participants were asked to fast for 2 hours before testing, to favor medication absorption. The institutional review board–approved study was registered on clinicaltrials.gov (No. 2013P-001857, Partners Healthcare IRB).

To exclude ineligible volunteers, vital signs were assessed (**Fig. 1**), and a urinary beta–human chorionic gonadotropin test excluded pregnancy in women who were not on reliable contraception and had their periods more than 2 weeks ago (N = 2). Participants then underwent baseline pain testing. Following this, a nurse dispensed the medication combination saying "this is the active medication or a placebo, it can often cause dry mouth or other mild symptoms, but this goes away quickly." The research pharmacy was in charge of the randomization order (created through a random numbers generator), and prepared the medication for each individual participant in matching gelatin capsules labeled "diclofenac 50 mg/placebo" and "atropine 0.6 mg/placebo." The placebo capsules were filled with microcrystalline cellulose. The study team in contact with participants (physicians, research assistants, and nurses) was blinded to the randomization order. Participants took 2 capsules of each medication or placebo per mouth with liquid. Participants were then taken to a waiting area, where they first filled questionnaires (expectations about relief, anxiety, optimism, depression, and anxiety sensitivity) during 15 minutes, followed by a 45-minute wait for the medication to become active. Salivary flow significantly decreases 50 minutes after administration of atropine;[22] peak anti-inflammatory activity starts at 60 minutes after the administration of diclofenac.[55] After 60 minutes waiting, participants were brought back to the examination room and reported—blindly to the researchers—(1) side effects on a standardized questionnaire,[42] (2) beliefs about treatment assignment on Likert scales (0 = definitely placebo, 1 = maybe placebo, 2 = fully uncertain, 3 = maybe medication, and 4 = definitely medication), and proceeded with the posttreatment pain sequence (outcomes presented in Table 2, supplementary materials, available online at http://links.lww.com/PAIN/A391). Finally, participants were debriefed regarding the actual randomization and the use of atropine (**Fig. 1**).

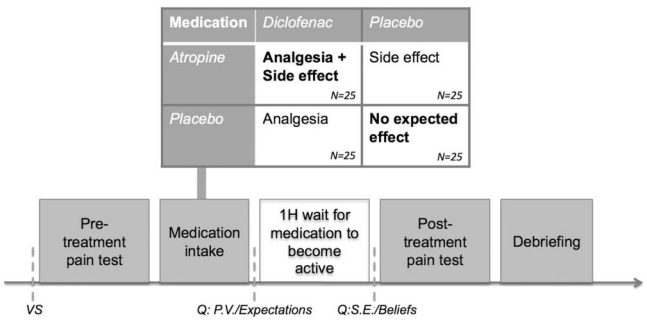

Figure 1. Study design and proceedings. Participants were only aware of the 2 boldened randomization groups, ie, diclofenac + atropine and placebo + placebo. VS, vital signs; Q, questionnaires; P.V., psychological variables; Expectations, measure of participant's expectations of relief; S.E., side effects; Beliefs, beliefs about treatment assignment.

2.3. Measures

2.3.1. Pain testing

Initial calibration identified the individual temperature eliciting moderate (Mod) pain ratings (mean visual analogue scale [VAS]

rating = 58 on a 100 mm scale, SD 12.9) and ascertained that Mod −2.5°C was minimally painful (mean VAS rating 8.7/100, SD 11.2). Mod −1.5° was perceived, on average, as low pain (mean VAS rating = 20.6/100, SD 10.9) and Mod −0.5°C was perceived as low-moderate (mean VAS rating = 39.2/100, SD 20.9) on an 8-second thermal stimulus applied to the left forearm (TSA-II; Medoc, Ramat Yishai, Israel).[32] The moderate stimulus was meant as the outcome of interest, with the other temperatures intended as distracters.[3] The pre- and post-treatment sequences consisted of the same sequence of 8 stimuli: low/minimal/Mod/low/Mod/near-moderate/Mod/low.

Subjects rated pain intensity of each stimulus on a 100-mm VAS (with anchors of "no pain" and "most intense pain imaginable")[26] during 20 to 35 seconds breaks in between stimuli.

2.3.2. Baseline characteristics

To control for possible confounders, expectations about relief ("How much relief do you personally expect to experience from this medication?"; VAS ranging from 0 = none to 100 = full pain relief), state anxiety (State-Trait Anxiety Inventory Scale [STAI-S]),[9] depression (BDI-II),[9] Anxiety Sensitivity Index (ASI),[41] and LOT optimism[50] were collected. All data were collected and managed using REDCap electronic data capture tools hosted at Partners Healthcare.[23]

2.4. Statistical analysis

The primary outcome was the reduction in moderate pain intensity after treatment (ie, analgesia, pretreatment minus posttreatment moderate pain ratings). We assessed the effect of diclofenac and atropine on pain reduction with a 2 × 2 (diclofenac × atropine) analysis of covariance (ANCOVA), with pretreatment moderate pain scores as the covariate. We hypothesized that atropine-induced dry mouth would lead participants to believe they were given active medication, thereby enhancing analgesia and explored this model through a mediation analysis. We also used 2 × 2 (diclofenac × atropine) analyses of variance (for continuous variables) and χ^2 (for sex) to assess age, sex, temperatures eliciting moderate pain, pretreatment moderate pain ratings, expectations of relief, anxiety sensitivity, state anxiety, dispositional optimism, and depression, as possible confounders. We used SPSS 22.0 to conduct analyses of variance, ANCOVAs, and χ^2 analyses, and Amos 22.0 to evaluate mediation (IBM, Armonk, NY).

3. Results

3.1. Analysis of covariance results

Randomized treatment groups did not differ significantly in age, sex, temperature eliciting moderate pain, pretreatment pain ratings, expected relief, state anxiety, anxiety sensitivity, optimism, or depression (**Table 1**).

The ANCOVA (diclofenac × atropine) on moderate pain ratings revealed a significant interaction, $F_{(1,95)} = 4.754$, $P = 0.032$, with no significant main effects (see group mean values in Table 2-supplementary materials, available online at http://links.lww.com/PAIN/A391). As illustrated in **Figure 2**, among participants given diclofenac, the addition of atropine increased pain relief more than 3-fold ($d = 0.77$); in contrast, the addition of atropine did not enhance the response to placebo ($d = 0.09$).

Previous studies have reported conflicting data concerning sex differences in NSAID and placebo analgesia.[3,9,13] For that reason, we conducted an additional ANCOVA on pain reduction, adding sex as a factor. Neither the main effect of sex nor any interaction involving sex reached significance.

3.2. Mediation analysis

We evaluated the hypothesized mediational chain using a two-group structural equation model, as shown in **Figure 3**. Because we had no hypotheses about how this mediated effect might differ across the diclofenac and no-diclofenac groups, all parameters (paths and error variances) were set equal across them. This model fits extremely well, χ^2 (6) = 6.476, $P = 0.372$, comparative fit index (CFI) = 0.983, root mean square error of approximation (RMSEA) = 0.028, pclose = 0.523. The estimates obtained, shown on the figure, indicate that all 3 legs of the mediation chain were statistically significant: atropine to dry mouth, dry mouth to belief about treatment, and belief about treatment to analgesia. In addition, a bias-corrected bootstrap test of the indirect effect represented by the combined sequence of these 3 paths was also statistically significant, $P = 0.008$ (standardized indirect effect = 0.026, 95% confidence interval = [0.006-0.073]).

Given the interaction finding in the ANCOVA, which suggests that there might possibly be process differences between the diclofenac and no-diclofenac groups, we also tested for a statistically significant difference between groups for each path in this model. The only difference that approached statistical significance was the direct effect of atropine on

Table 1

Participant pretreatment characteristics.

	Atropine + diclofenac (n = 25), M (SD)	Atropine + placebo (n = 25), M (SD)	Placebo + diclofenac (n = 25), M (SD)	Placebo + placebo (n = 25), M (SD)	Sig.
Age, y	24.48 (5.08)	24.12 (4.83)	23.52 (4.48)	23.16 (3.94)	$P > 0.5$
% Female	48	44	56	56	$P > 0.5$
Calibration for moderate pain, °C	46.26 (1.6)	47.16 (0.99)	46.68 (1.28)	46.48 (1.58)	$P = 0.13$
Pretreatment moderate pain ratings (VAS/100)	59.6 (13.9)	57.5 (11.6)	60.9 (11.8)	54.0 (13.9)	$P = 0.25$
Expected relief (VAS/100)	60.09 (23.59)	65.48 (19.13)	59.04 (20.08)	60.79 (17.37)	$P > 0.5$
ASI	12.92 (5.64)	13.08 (6.49)	11.48 (6.54)	13.28 (7.75)	$P > 0.5$
STAI-S	30.8 (6.08)	33.2 (10.33)	29.40 (7.50)	28.44 (7.49)	$P = 0.18$
LOT	7.16 (4.46)	6.88 (4.29)	6.36 (5.86)	7.4 (3.40)	$P > 0.5$
BDI	4.2 (3.83)	3.52 (3.85)	4.24 (5.48)	3.96 (5.21)	$P > 0.5$

ASI, Anxiety Sensitivity Index; BDI, Beck Depression Index; LOT, Life orientation Test (optimism); STAI-S, State-Trait Anxiety Inventory-State Scale; VAS, visual analogue scale.

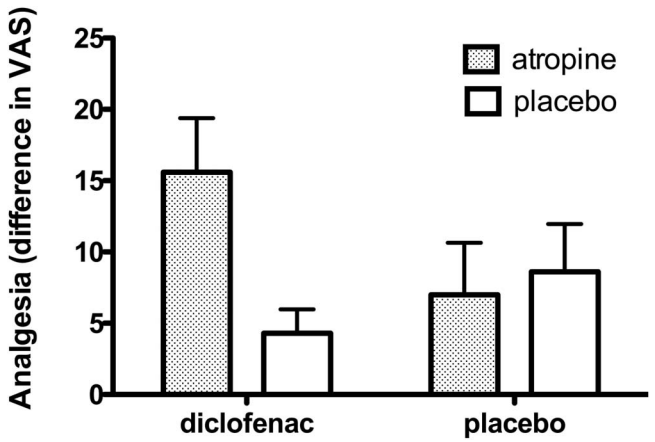

Figure 2. Effects of diclofenac and atropine on pain relief. The levels of analgesia, defined as the difference between pretreatment minus posttreatment pain ratings, are illustrated for the 4 treatment groups. Diclofenac is an NSAID reducing heat pain; atropine, an antimuscarinic agent without known analgesic effects, was given to induce a side effect in the form of dry mouth. Error bars = SEM. NSAID, nonsteroidal anti-inflammatory drug; VAS, visual analogue scale.

analgesia, $\chi^2(1) = 3.715$, $P = 0.054$. For those given diclofenac, there was a significant direct effect of atropine on analgesia, yielding a standardized path of 0.28, $P = 0.039$, whereas there was no such effect for those not given diclofenac, standardized path = −0.09, $P = 0.539$. We also used the Bayesian custom-estimand approach in Amos to test for moderated mediation—that is, whether the mediational chain differed significantly across the 2 groups; it did not ($P = 0.75$). Thus, the 2 groups seem to have differed only in the direct effect of atropine on analgesia, and not in the mediational chain.

4. Discussion

To our knowledge, we provide the first experimental test of how the perception of side effects in an analgesic RCT affects beliefs about treatment assignment, which in turn increases the response to the medication. Our mediation analysis confirmed the hypothesis that atropine increased the perception of side effects, which led to enhanced beliefs that one had received the active medication, in turn enhancing analgesia. We also hypothesized an additive relation between placebo and drug effects, such that altering expectations would impact the response to both active drug and placebo, increasing the placebo response and masking drug–placebo differences.[48,58] Instead, the ANCOVA revealed a significant interaction. In fact, the difference between diclofenac and placebo was significant only when atropine had been added. The mean difference between diclofenac + atropine and placebo + atropine was 11.32 on a 100-mm VAS. This can be compared with the mean drug–placebo difference of 8.39 reported in a Cochrane review of the effects of NSAIDs on low back pain.[46]

The tests for differences between the diclofenac and no-diclofenac groups for each path in the mediational model might provide clues to understand these findings. There was a nearly significant ($P = 0.054$) between-group difference in the direct path from atropine to analgesia. For participants given diclofenac, there was a significant direct effect of atropine on analgesia ($P = 0.039$), whereas there was no such effect for those not given diclofenac, which is consistent with the interaction observed in the ANCOVA. These data suggest that atropine and diclofenac may work synergistically in the relief of pain. These data need to be interpreted cautiously, as the significance of the between group difference was marginal. However, tests of moderator effects have notoriously low power, leading many statisticians to recommend using higher than conventional alpha levels for them.[21]

How could one explain the apparent synergistic effect of diclofenac and atropine? A possible explanation can be derived from two separately well-established findings. First, placebo analgesia can be blocked by naloxone, an opioid antagonist, supporting that placebo analgesia is partially mediated by the release of endogenous opioids.[1,19,31] Second, an analgesic synergy between exogenous opioids and NSAIDs, including diclofenac, has been reported both in humans[35] and animal models.[37,38,56] Thus, we hypothesize that diclofenac could potentiate the analgesic effects of endogenous opioids in a manner that is similar to the way that NSAIDs potentiate the analgesic effects of exogenous opioids. In sum, the beliefs about treatment assignment that were indirectly induced by atropine (**Fig. 3**) may have stimulated the release of endogenous opioids, which were then potentiated by diclofenac.

An alternative explanation could be inherent to our model: We chose a measure of beliefs about medication attribution, hence capturing one factor of expectancy. Yet, predictions about the future involve multiple cognitive processes, leaving a number unaccounted for by our model.[12] In fact, we did not collect measures for all conscious processes that could have interacted with embodied predictions, such as fear, attention, therapeutic alliance, or recall of previous somatic experiences.[5,16] Furthermore, nonconscious processes, which are complex to measure, have been shown to induce placebo effects, and could also have been involved through the sensory nature of our expectancy manipulation.[24,25,47] Therefore, the unmediated effects of atropine on analgesia in the diclofenac group might be related to unmeasured processes that were affected by the presence of an active drug.

Interesting parallels can be made with recent publications. In a clinical RCT of amitriptyline for pain, expectations about treatment outcomes correlated with analgesia only in the real treatment group.[57] Also, in an experimental model of relief from heat pain using lidocaine cream, enhanced expectation-induced placebo analgesia was only found in the active treatment group.[51] For both these studies, there is direct[57] or indirect[29] evidence that participants were in fact unblinded to their treatment allocation, due to various drug effects. Of interest, both these studies used a treatment that had shown little efficacy for the investigated pain conditions in relevant separate clinical trials[14] and experimental studies.[2,29] This suggests that a signal of "being on active

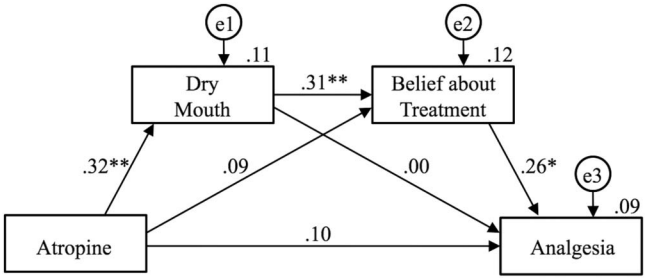

Figure 3. Structural equation model predicting analgesia. Standardized estimates are shown on the paths connecting the variables, and proportions of variance accounted for in each variable are shown above each variable box. The variables shown in circles represent unexplained variance in each measured variable. *$P < 0.05$. **$P < 0.01$.

medication" could boost the efficacy of a treatment that has small effect sizes.

We found that the mediational model from atropine to dry mouth, from dry mouth to the belief that one has been given the active analgesic, and from this belief to analgesia was well supported by the mediation analysis. Somewhat surprisingly, in view of the interaction found in ANCOVA analysis, the mediational chain did not differ significantly across the 2 groups ($P = 0.75$). Mediation models can have substantially greater power than other types of analysis,[27] and here the model detected a relation of atropine to analgesia in the no-diclofenac group that was not apparent in the ANCOVA. Instead, the 2 groups seem to have differed only in the direct effect of atropine on analgesia, and not in the mediational chain. These data support the hypothesis that the perception of side effects might artifactually enhance drug–placebo differences in conventional clinical trials. To control for this possibility, the use of active placebos to protect blinding might be considered more frequently.

Our sample included both sexes, without significant effects of sex on analgesia. There are contradictory reports in the literature regarding sex differences in analgesia through NSAIDs. A large study (195F/119M) on molar dental extraction showed no difference,[6] whereas smaller studies on experimental pain models such as electrical stimuli ($n = 20$)[13] or cold pressor test ($n = 50$)[18] suggest sex differences in NSAID and placebo differences, yet with conflicting results. Larger samples might be needed to clarify this debate.

This study has some limitations, inherent to its design. Participants were healthy volunteers, and replication with a clinical sample would be warranted. A similar trial in a larger population, possibly with an analgesic that has stronger effects on the chosen pain model, would also be helpful. However, this requirement is a challenge, knowing the limitations in potency of analgesics for acute pain[39] and the possibility for negative expectations to fully block the effects of a strong opiate such as remifentanil.[11] A blinding of the treating physician to the deception could also be considered, although practically difficult to carry through. Finally, if the demonstrated effect is universal or only applicable to specific situations, such as NSAIDs, requires more research.

In conclusion, these findings could have important implications for the design of RCTs, because the double-blind nature of an RCT instills uncertainty in subjects regarding whether they received the active drug or placebo. Side effects may reduce uncertainty in active drug arms, thereby enhancing drug–placebo differences. This comes at a time when RCT methodology is being questioned in the light of placebo research.[10,30,33,59,64] These experimental findings warrant replication in clinical populations. The possibility of a synergy between diclofenac and endogenous opioids in the context of a placebo effect could also be investigated further.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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This manuscript is original work that has not been previously published. The abstract has been accepted for a poster presentation at the 2016 World congress on Pain, meeting of the IASP, September 26 to 29, 2016, Yokohama, Japan.

C. Berna and I. Kirsch had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Research Resources, the National Center for Advancing Translational Science, or the National Institutes of Health.

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Appendix A. Supplemental Digital Content

Supplemental Digital Content associated with this article can be found online at http://links.lww.com/PAIN/A391.

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References

[1] Amanzio M, Pollo A, Maggi G, Benedetti F. Response variability to analgesics: a role for non-specific activation of endogenous opioids. PAIN 2001;90:205–15.
[2] Aslaksen PM, Zwarg ML, Eilertsen HI, Gorecka MM, Bjorkedal E. Opposite effects of the same drug: reversal of topical analgesia by nocebo information. PAIN 2015;156:39–46.
[3] Atlas LY, Bolger N, Lindquist MA, Wager TD. Brain mediators of predictive cue effects on perceived pain. J Neurosci 2010;30:12964–77.
[4] Atlas LY, Whittington RA, Lindquist MA, Wielgosz J, Sonty N, Wager TD. Dissociable influences of opiates and expectations on pain. J Neurosci 2012;32:8053–64.
[5] Atlas LY, Wielgosz J, Whittington RA, Wager TD. Specifying the non-specific factors underlying opioid analgesia: expectancy, attention, and affect. Psychopharmacology (Berl) 2014;231:813–23.
[6] Averbuch M, Katzper M. A search for sex differences in response to analgesia. Arch Intern Med 2000;160:3424–8.
[7] Baethge C, Assall OP, Baldessarini RJ. Systematic review of blinding assessment in randomized controlled trials in schizophrenia and affective disorders 2000-2010. Psychother Psychosom 2013;82:152–60.
[8] Bausell RB, Lao L, Bergman S, Lee WL, Berman BM. Is acupuncture analgesia an expectancy effect? Preliminary evidence based on participants' perceived assignments in two placebo-controlled trials. Eval Health Prof 2005;28:9–26.
[9] Beck AT, Steer RA, Brown GK. Manual for the beck depression inventory-II. San Antonio: Psychological Corporation, 1996.
[10] Benedetti F, Carlino E, Piedimonte A. Increasing uncertainty in CNS clinical trials: the role of placebo, nocebo, and Hawthorne effects. Lancet Neurol 2016;15:736–47.
[11] Bingel U, Wanigasekera V, Wiech K, Ni Mhuircheartaigh R, Lee MC, Ploner M, Tracey I. The effect of treatment expectation on drug efficacy:

imaging the analgesic benefit of the opioid remifentanil. Sci Transl Med 2011;3:70ra14.
[12] Bubic A, Von Cramon DY, Schubotz R. Prediction, cognition and the brain. Front Hum Neurosci 2010;4:25.
[13] Butcher BE, Carmody JJ. Sex differences in analgesic response to ibuprofen are influenced by expectancy: a randomized, crossover, balanced placebo-designed study. Eur J Pain 2012;16:1005–13.
[14] Cardenas DD, Warms CA, Turner JA, Marshall H, Brooke MM, Loeser JD. Efficacy of amitriptyline for relief of pain in spinal cord injury: results of a randomized controlled trial. PAIN 2002;96:365–73.
[15] Chen JA, Papakostas GI, Youn SJ, Baer L, Clain AJ, Fava M, Mischoulon D. Association between patient beliefs regarding assigned treatment and clinical response: reanalysis of data from the Hypericum Depression Trial Study Group. J Clin Psychiatry 2011;72:1669–76.
[16] Clark A. Embodied prediction. In: Metzinger TK, Windt JM, editors. Open MIND. Frankfurt am Main: MIND Group, 2015.
[17] Colloca L, Lopiano L, Lanotte M, Benedetti F. Overt versus covert treatment for pain, anxiety, and Parkinson's disease. Lancet Neurol 2004; 3:679–84.
[18] Compton P, Charuvastra VC, Ling W. Effect of oral ketorolac and gender on human cold pressor pain tolerance. Clin Exp Pharmacol Physiol 2003; 30:759–63.
[19] Eippert F, Bingel U, Schoell ED, Yacubian J, Klinger R, Lorenz J, Buchel C. Activation of the opioidergic descending pain control system underlies placebo analgesia. Neuron 2009;63:533–43.
[20] Enck P, Klosterhalfen S, Weimer K, Horing B, Zipfel S. The placebo response in clinical trials: more questions than answers. Philos Trans R Soc Lond B Biol Sci 2011;366:1889–95.
[21] Frazier PA, Tix AP, Barron KE. Testing moderator and mediator effects in counseling psychology research. J Couns Psychol 2004;51:115.
[22] Fry JR, Burr SA. A double-blind atropine trial for active learning of autonomic function. Adv Physiol Educ 2011;35:438–44.
[23] Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42:377–81.
[24] Jensen KB, Kaptchuk TJ, Chen X, Kirsch I, Ingvar M, Gollub RL, Kong J. A neural mechanism for nonconscious activation of conditioned placebo and nocebo responses. Cereb Cortex 2015;25:3903–10.
[25] Jensen KB, Kaptchuk TJ, Kirsch I, Raicek J, Lindstrom KM, Berna C, Gollub RL, Ingvar M, Kong J. Nonconscious activation of placebo and nocebo pain responses. Proc Natl Acad Sci USA 2012;109:15959–64.
[26] Jensen MP, Karoly P, Braver S. The measurement of clinical pain intensity: a comparison of six methods. PAIN 1986;27:117–26.
[27] Kenny DA, Judd CM. Power anomalies in testing mediation. Psychol Sci 2014;25:334–9.
[28] Kirsch I, Rosadino MJ. Do double-blind studies with informed consent yield externally valid results? An empirical test. Psychopharmacology (Berl) 1993;110:437–42.
[29] Krumova EK, Zeller M, Westermann A, Maier C. Lidocaine patch (5%) produces a selective, but incomplete block of Adelta and C fibers. PAIN 2012;153:273–80.
[30] Kube T, Rief W. Are placebo and drug-specific effects additive? Questioning basic assumptions of double-blinded randomized clinical trials and presenting novel study designs. Drug Discov Today 2017. doi: 10.1016/j.drudis.2016.11.022. [Epub ahead of print].
[31] Levine J, Gordon N, Fields H. The mechanism of placebo analgesia. Lancet 1978;312:654–7.
[32] Loggia ML, Jensen K, Gollub RL, Wasan AD, Edwards RR, Kong J. The catechol-O-methyltransferase (COMT) val158met polymorphism affects brain responses to repeated painful stimuli. PLoS One 2011;6:e27764.
[33] Lund K, Vase L, Petersen GL, Jensen TS, Finnerup NB. Randomised controlled trials may underestimate drug effects: balanced placebo trial design. PLoS One 2014;9:e84104.
[34] Margraf J, Ehlers A, Roth WT, Clark DB, Sheikh J, Agras WS, Taylor CB. How "blind" are double-blind studies? J Consult Clin Psychol 1991;59: 184–7.
[35] Marret E, Kurdi O, Zufferey P, Bonnet F. Effects of nonsteroidal antiinflammatory drugs on patient-controlled analgesia morphine side effects: meta-analysis of randomized controlled trials. Anesthesiology 2005;102:1249–60.
[36] Max MB, Schafer SC, Culnane M, Dubner R, Gracely RH. Association of pain relief with drug side effects in postherpetic neuralgia: a single-dose study of clonidine, codeine, ibuprofen, and placebo. Clin Pharmacol Ther 1988;43:363–71.
[37] Miranda HF, Pinardi G. Lack of effect of naltrindole on the spinal synergism of morphine and non-steroidal anti-inflammatory drugs (NSAIDS). J Physiol Pharmacol 2009;60:71–6.
[38] Miranda HF, Prieto JC, Pinardi G. Spinal synergy between nonselective cyclooxygenase inhibitors and morphine antinociception in mice. Brain Res 2005;1049:165–70.
[39] Moore RA, Derry S, McQuay HJ, Wiffen PJ. Single dose oral analgesics for acute postoperative pain in adults. Cochrane Database Syst Rev 2011;Cd008659.
[40] Papakostas GI, Fava M. Does the probability of receiving placebo influence clinical trial outcome? A meta-regression of double-blind, randomized clinical trials in MDD. Eur Neuropsychopharmacol 2009;19: 34–40.
[41] Reiss S, Peterson RA, Gursky DM, McNally RJ. Anxiety sensitivity, anxiety frequency and the prediction of fearfulness. Behav Res Ther 1986;24: 1–8.
[42] Rief W, Barsky AJ, Glombiewski JA, Nestoriuc Y, Glaesmer H, Braehler E. Assessing general side effects in clinical trials: reference data from the general population. Pharmacoepidemiol Drug Saf 2011;20:405–15.
[43] Rief W, Bingel U, Schedlowski M, Enck P. Mechanisms involved in placebo and nocebo responses and implications for drug trials. Clin Pharmacol Ther 2011;90:722–6.
[44] Rief W, Glombiewski JA. The hidden effects of blinded, placebo-controlled randomized trials: an experimental investigation. PAIN 2012; 153:2473–7.
[45] Rief W, Nestoriuc Y, Weiss S, Welzel E, Barsky AJ, Hofmann SG. Meta-analysis of the placebo response in antidepressant trials. J Affect Disord 2009;118:1–8.
[46] Roelofs PD, Deyo RA, Koes BW, Scholten RJ, van Tulder MW. Non-steroidal anti-inflammatory drugs for low back pain. Cochrane Database Syst Rev 2008;CD000396.
[47] Rosen A, Yi J, Kirsch I, Kaptchuk TJ, Ingvar M, Jensen KB. Effects of subtle cognitive manipulations on placebo analgesia—an implicit priming study. Eur J Pain 2016. doi: 10.1002/ejp.961. [Epub ahead of print].
[48] Rutherford BR, Roose SP. A model of placebo response in antidepressant clinical trials. Am J Psychiatry 2013;170:723–33.
[49] Rutherford BR, Sneed JR, Roose SP. Does study design influence outcome? The effects of placebo control and treatment duration in antidepressant trials. Psychother Psychosom 2009;78:172–81.
[50] Scheier MF, Carver CS, Bridges MW. Distinguishing optimism from neuroticism (and trait anxiety, self-mastery, and self-esteem): a reevaluation of the life orientation test. J Pers Soc Psychol 1994;67:1063–78.
[51] Schenk LA, Sprenger C, Geuter S, Buchel C. Expectation requires treatment to boost pain relief: an fMRI study. PAIN 2014;155:150–7.
[52] Shah E, Triantafyllou K, Hana AA, Pimentel M. Adverse events appear to unblind clinical trials in irritable bowel syndrome. Neurogastroenterol Motil 2014;26:482–8.
[53] Sinyor M, Levitt AJ, Cheung AH, Schaffer A, Kiss A, Dowlati Y, Lanctot KL. Does inclusion of a placebo arm influence response to active antidepressant treatment in randomized controlled trials? Results from pooled and meta-analyses. J Clin Psychiatry 2010;71:270–9.
[54] Sneed JR, Rutherford BR, Rindskopf D, Lane DT, Sackeim HA, Roose SP. Design makes a difference: a meta-analysis of antidepressant response rates in placebo-controlled versus comparator trials in late-life depression. Am J Geriatr Psychiatry 2008;16:65–73.
[55] Stacher G, Steinringer H, Schneider S, Mittelbach G, Winklehner S, Gaupmann G. Experimental pain induced by electrical and thermal stimulation of the skin in healthy man: sensitivity to 75 and 150 mg diclofenac sodium in comparison with 60 mg codeine and placebo. Br J Clin Pharmacol 1986;21:35–43.
[56] Torres-Lopez JE, Carmona-Diaz E, Cortes-Penaloza JL, Guzman-Priego CG, Rocha-Gonzalez HI. Antinociceptive synergy between diclofenac and morphine after local injection into the inflamed site. Pharmacol Rep 2013;65:358–67.
[57] Turner JA, Jensen MP, Warms CA, Cardenas DD. Blinding effectiveness and association of pretreatment expectations with pain improvement in a double-blind randomized controlled trial. PAIN 2002;99:91–9.
[58] Tuttle AH, Tohyama S, Ramsay T, Kimmelman J, Schweinhardt P, Bennett GJ, Mogil JS. Increasing placebo responses over time in U.S. clinical trials of neuropathic pain. PAIN 2015;156:2616–26.
[59] Vase L, Amanzio M, Price DD. Nocebo vs. Placebo: the challenges of trial design in analgesia research. Clin Pharmacol Ther 2015;97:143–50.
[60] Vase L, Baram S, Takakura N, Yajima H, Takayama M, Kaptchuk TJ, Schou S, Jensen TS, Zachariae R, Svensson P. Specifying the nonspecific components of acupuncture analgesia. PAIN 2013;154: 1659–67.
[61] Waber RL, Shiv B, Carmon Z, Ariely D. Commercial features of placebo and therapeutic efficacy. JAMA 2008;299:1016–17.
[62] Walsh BT, Seidman SN, Sysko R, Gould M. Placebo response in studies of major depression: variable, substantial, and growing. JAMA 2002;287: 1840–7.

[63] Weimer K, Colloca L, Enck P. Placebo effects in psychiatry: mediators and moderators. Lancet Psychiatry 2015;2:246–57.
[64] Weimer K, Enck P. Traditional and innovative experimental and clinical trial designs and their advantages and pitfalls. Handb Exp Pharmacol 2014;225:237–72.
[65] Wise RA, Bartlett SJ, Brown ED, Castro M, Cohen R, Holbrook JT, Irvin CG, Rand CS, Sockrider MM, Sugar EA; American Lung Association Asthma Clinical Research Centers. Randomized trial of the effect of drug presentation on asthma outcomes: the American Lung Association Asthma Clinical Research Centers. J Allergy Clin Immunol 2009;124:436–44, 444e431–438.