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Expectations for improvement: a neglected but potentially important covariate or moderator for chronic pain clinical trials

Dale J. Langford[1,2,3,*,**], **Raissa Lou**[2,*], **Soun Sheen**[2], **Dagmar Amtmann**[3], **Luana Colloca**[4], **Robert R. Edwards**[5], **John T. Farrar**[6], **Nathaniel P. Katz**[7], **Michael P. McDermott**[2], **Bryce B. Reeve**[8], **Ajay D. Wasan**[9], **Dennis C. Turk**[3], **Robert H. Dworkin**[2], **Jennifer S. Gewandter**[2]

[1]Hospital for Special Surgery, New York, NY, USA

[2]University of Rochester, Rochester, NY

[3]University of Washington, Seattle WA, USA

[4]University of Maryland, Baltimore, MD, USA

[5]Harvard Medical School, Boston, MA, USA

[6]University of Pennsylvania, Philadelphia, PA, USA

[7]Tufts University and Analgesic Solutions, Boston, MA, USA

[8]Duke University School of Medicine, Durham, NC, USA

[9]University of Pittsburgh, Pittsburgh, PA, USA

Abstract

Variability in pain-related outcomes can hamper assay sensitivity of chronic pain clinical trials. Expectations of outcome in such trials may account for some of this variability, and thereby impede development of novel pain treatments. Measurement of participants' expectations prior to initiating study treatment (active or placebo) is infrequent, variable, and often unvalidated. Efforts to optimize and standardize measurement, analysis, and management of expectations are needed. In this Focus Article, we provide an overview of research findings on the relationship between baseline expectations and pain-related outcomes in clinical trials of pharmacological and non-pharmacological pain treatments. We highlight the potential benefit of adjusting for participants' expectations in clinical trial analyses and draw on findings from patient interviews to discuss critical issues related to measurement of expectations. We conclude with suggestions regarding future studies focused on better understanding the utility of incorporating these measures into clinical trial analyses.

Perspective—This focus article provides an overview of the relationship between participants' baseline expectations and pain-related outcomes in the setting of clinical trials of chronic pain

[**]Corresponding Author: Dale J. Langford, PhD, Department of Anesthesiology, Critical Care & Pain Management, Hospital for Special Surgery, 535 E 70th St, New York, NY 10021, Phone: 212-774-7583.

[*]Co-first authors.

treatments. Systematic research focused on the measurement of expectations and the impact of adjusting for expectations in clinical trial analyses may improve assay sensitivity.

Keywords

outcome expectations; chronic pain; clinical trials; covariate adjustment; assay sensitivity

1. Introduction

Currently available analgesics for chronic pain are only moderately effective and, in practice, provide little to no relief for many patients. Development of novel analgesics has proven challenging, with decreasing treatment effect sizes observed in recent randomized clinical trials (RCTs), even for drugs with known efficacy.[15, 36] High variability in pain ratings and substantial placebo group responses (i.e., reduction in pain intensity ratings among control group participants exposed to a placebo/"sham" treatment) can hamper assay sensitivity of these trials.[11] One factor that could contribute to high variability of outcomes and to placebo group responses is participants' outcome expectations (i.e., one's prediction or belief about the outcome of receiving a treatment).[5] While evidence suggests that expectations account for some of the variability of outcomes after analgesic and placebo treatments (e.g.,[21, 28]), evaluation of and adjustment for participants' outcome expectations in pain clinical trials is infrequent. Efforts to optimize, standardize, and validate measures of outcome expectations for use (and analysis) in chronic pain clinical trials are needed.[6]

In this Focus Article, we summarize evidence for the relationship between baseline expectations and outcome after analgesic or placebo treatments, discuss the potential advantages of including baseline outcome expectations for change in pain as a covariate in chronic pain RCTs, discuss some measurement issues revealed through concept elicitation interviews among patients with chronic pain, and outline important next steps.

2. Evidence of association between expectation and pain-related outcomes in clinical trials of pain treatments clinical trials for chronic pain

Several studies have evaluated the relationship between baseline expectations of pain relief or functional improvement and outcomes of chronic pain interventions. Many of these studies focused on acupuncture,[2, 3, 28, 34, 41] physical therapy (e.g., dry needling,[18] or manual therapy[21, 31]) for the treatment of musculoskeletal disorders (e.g., back pain, osteoarthritis). These trials included a variety of assessments of expectations of outcomes, most often a single item that asked participants about how much improvement they expected in their condition in general (regardless of treatment group assignment) or with regard to specific treatment(s) under investigation. Several studies revealed that positive expectations were associated with significantly better patient-reported outcomes, including greater reduction in pain,[19, 21, 28, 38, 41, 45] greater improvement in function,[21] greater probability of recovery,[31] and a more favorable global perceived effect of treatment,[3, 19, 21] compared with neutral or negative expectations. Studies that evaluated the interaction between treatment assignment and expectations revealed either that the expectation-outcome association occurred with active, but not placebo treatment[38, 41] or that the interaction was

not significant.[21, 45] In contrast, experimental modifications of expectations (e.g., neutral vs. positive drug presentation) have been shown to have greater effects on outcomes in placebo than active treatment groups.[24, 44] Other studies have demonstrated associations between expectations and some but not all outcomes,[17, 18, 20, 23] or no significant association[30] between treatment expectations and outcomes. Taken together, the variability in both measurement of expectations and in the outcomes evaluated preclude any clear conclusions about the impact of expectations on outcomes in currently available chronic pain trials investigating these relationships. Of note, while the relationship between expectations and outcome has been explored, the inclusion of expectations as a pre-specified covariate in analyses of RCT data is very infrequent.

3. Benefits of covariate adjustment in analyses of clinical trial data

The FDA and EMA both suggest pre-specified adjustment for baseline covariates that are likely associated with trial outcomes to increase the precision of treatment effect estimates and thus increase trial assay sensitivity (or ability to detect a true treatment response).[14, 40] Therefore, given the evidence summarized above, it is reasonable to hypothesize that adjustment for baseline expectations may improve assay sensitivity. Inclusion of a baseline assessment of expectations in clinical trials would also make it possible to examine whether baseline expectations moderate analgesic treatment effect sizes (e.g., examine whether the magnitude of the difference between treatment groups varies as a function of participants' baseline expectations). Measurement of expectations across multiple clinical trials could provide data to investigate whether adjustment for baseline expectations does in fact increase precision (and therefore assay sensitivity) in clinical trials and whether baseline expectations do, in fact, moderate clinical trial outcomes. Consistently-identified moderation effects would support the utility of strategies to modify participant expectations in clinical trials (e.g.,[24, 44]), justifying randomized studies to evaluate the utility of specific strategies.

To this end, a valid assessment of baseline expectations and systematic investigation of the relationships between expectations and outcomes are needed. A brief, valid and reliable measure of outcome expectations in the context of chronic pain clinical trials could promote uptake in clinical trials, and thus provide the data necessary to evaluate the benefits of adjusting for expectations in the analyses of chronic pain clinical trials.

4. Measurement of expectations

How expectations should be assessed is not clear, as considerable heterogeneity remains in their definition and measurement. Multiple patient-reported measures exist to assess outcome expectations (e.g., see [1] for systematic review); however, many measures are either quite lengthy, thereby prohibiting their use in clinical trials where expectations are not the primary outcome (e.g., 35-item Treatment Expectation Questionnaire[1]), not worded appropriately for chronic pain that is unlikely to "completely" resolve (e.g., Stanford Expectations of Treatment Scale[46]), and/or do not incorporate the possibility of receiving placebo treatment (e.g., "this treatment" may refer to active or placebo treatment[9, 46]). Of note, a prior qualitative study identified modifications to the generic Credibility/Expectancy

Questionnaire (CEQ) that were necessary to ensure content validity among patients with chronic pain in the setting of rehabilitative therapy.[29]

With some exceptions (e.g., CEQ), clinical trials of pain treatments have predominantly included unvalidated and variably worded single-item questions (e.g., "How helpful do you believe [treatment X] would be for your current back problems?"[23]). Measures also vary in terms of response options (e.g., 0 – 10 numeric rating scales for expected improvement,[17, 19, 23] expected pain intensity,[41] likelihood of recovery,[31] 0% - 100% for expected pain relief,[38] "much worse / worse / a little worse/ the same / better / much better"[18]). Given that we lack evidence for how these questions might be interpreted, and what factors or experiences might influence expectations, it is critical that we include patient perspectives.[8, 26] A more defined patient-centered conceptualization of expectations, particularly as they pertain to clinical trial outcomes in chronic pain, is essential to inform valid assessment.

4.1 A qualitative exploration of expectation measurement

Given that (1) the literature suggests that adjusting for baseline expectations may improve assay sensitivity, (2) little is known about patients' interpretation of questions about expectations, (3) there is inconsistency in the literature on measures of expectations, and (4) evaluating the patient perspective is recommended as an initial step in the development of new measurement tools (e.g., by regulatory agencies, such as FDA[39]), we conducted an exploratory qualitative inquiry into how patients with chronic pain rate outcome expectations in the context of a hypothetical clinical trial. We conducted semi-structured qualitative interviews among 22 individuals with a wide range of chronic pain conditions over a 3-month period. The study was approved by the University of Rochester RSRB. All interviews were done by a single trained interviewer (R.L.). English-speaking adults who had experienced chronic pain for at least 3 months prior, which was verified through medical records, were eligible to participate in the study. All participants were compensated monetarily ($50) upon interview completion. Participants self-reported age, gender, race, and level of education at the outset of the interview. Participants ranged in age from 25 to 76 years old (M = 51.8; SD =16.9). The sample was 68% female; 5% Asian, 14% Black or African American, 73% White, and 9% mixed race (i.e., endorsed two or more racial groups) or unknown; 5% had less than a high school degree, 32% were high school graduates, and 50% and 14% obtained a college or graduate degree, respectively.

During the interviews, participants were presented with a hypothetical scenario that asked them to imagine that they were starting a clinical trial for a new treatment for their chronic pain condition, with equal chance of receiving a placebo or active treatment. Interview questions evaluated participant feedback on single-item questions designed to rate "study treatment" outcome expectations, as well as what factors participants perceived as contributing to their expectation ratings. Participants were introduced to the concept of a randomized clinical trial with 50% chance of receiving active treatment or placebo and then asked to rate their expectations for a change in pain after receiving "study treatment" (i.e., active or placebo). Participants were intentionally not asked to rate expectations of group assignment and outcome of active treatment separately because the construct that is

important to assess for the purposes of predicting outcomes in a clinical trial is participant expectations of outcome in the context of the possibility of receiving a placebo. Consensus on which specific question(s) best captured study treatment expectations was not achieved; however, interviews, which included a "think-aloud" technique (used to gauge insight into an individual's cognitive processing[10, 42, 43]), revealed several themes regarding those factors that contributed to participants' expectations for outcome. To enact the think-aloud portion of the interviews, the single interviewer (R.L.) instructed participants to verbalize their thought processes while answering each interview question. To provide clarity on this technique, participants were presented with an example scenario/question. The example scenario and question were as follows: "Imagine you are going to eat at a brand-new Italian restaurant that just opened downtown and someone then asks you the following question: "After eating at this, I expect to feel [response options]: 'Very satisfied and will want to eat here again as soon as possible', 'Satisfied', 'Neutral', 'Okay, but I probably won't eat here again', or 'I want my money back'. The interviewer then demonstrated the following example think-aloud process for what they might be thinking while answering the example question: "I expect that I will feel satisfied because this restaurant is brand new, which is often a promising sign, and I like to try new things. I also love Italian food, so I expect to at least enjoy the meal somewhat, but trying a completely new place can also be risky and I might not like it." This think-aloud technique was used to more accurately capture all the factors that contribute to and shape an individual's outcome expectations, whereas having participants answer multiple scripted questions about expectations or participating in focus group discussions may not have provided this rich and more personal information.

A content analysis based on participants' responses was conducted using audio-recordings of all interviews. Direct quotes from participants in response to each question were extracted by the single reviewer (R.L.) and preliminary concepts identified. The number and types of conceptual categories were finalized through discussion of direct quotes among three authors (R.L., J.S.G., and D.J.L). The number of participants who endorsed a conceptual category (i.e., made relevant direct quote) was then tallied by R.L. For the think-aloud portion of interviews, three common concepts were identified: (1) balance between hope and realistic expectations for treatment efficacy (n=17; 77%; e.g., "I'm optimistic, but don't expect full relief"), hope for treatment efficacy (n=13; 59%, e.g., "I'm hoping that it gives some relief"); and evidence of experimental efficacy (n=6, 27%, e.g., "You said that the research has shown that the new drug has been shown to be effective at reducing chronic pain"). Interestingly, either using think-aloud or a probing follow-up question, the majority of participants (64%) did not factor in the possibility of receiving the placebo treatment when considering how to rate their expectations (e.g., "my mind didn't go there [placebo], no"; "I always just assume I am not getting the placebo"; "I'm hoping that I get the real thing"). If this finding generalizes to real clinical trial settings, it suggests that participants' expectations are commonly based on the assumption (or hope) that they will receive the active treatment, disregarding the possibility of assignment to placebo. Mitigating this assumption of treatment assignment may serve to decrease expectations, which could reduce improvements in subjective outcomes in the placebo group of clinical trials (and thereby improve assay sensitivity) (e.g., [24, 44]). However, given findings that expectations

are uniquely associated with active treatment group outcomes,[20, 38, 41] attenuating baseline expectations could potentially have a neutral or even harmful effect on assay sensitivity.

Participants noted a number of factors when asked what contributed to their expectations for pain treatment (Figure 1). Personal experience with previous pain treatments and existing research on the specific pain treatment were most commonly reported (each by 12 participants; 55%). Participants also considered their doctor's knowledge (n=5; 23%), noted a willingness to be open-minded about treatment (n=4; 18%), and highlighted the importance of a clear understanding of the treatment, the type of drug, the doctor's opinion or belief in the treatment, and hopefulness (all 14%). That participants were less likely to verbalize "hopefulness" as a contributing factor for expectations than when they described their thinking while rating their expectations (14% vs 59%) reinforces the added value of incorporating a "think-aloud" approach. Other less prevalent factors included acquaintances' treatment experience, current pain state, relationship with their doctor, side effects, positive thinking, and treatment novelty (all 5%).

5. Conclusions, considerations, and future directions

Taken together, these findings highlight the heterogeneous factors surrounding the construct of outcome expectations in the context of chronic pain clinical trials, as well as the impact of the individual's unique perspectives and considerations, some of which may be unconsciously formulated,[22] and therefore outside the realm of patient-reported measurement. This observation is aligned with evidence from studies of outcome expectations in the context of psychotherapy,[7] in which outcome expectations may be delineated as overt or "cognitive" expectations (e.g., influenced by doctor's opinion or research findings as noted in our study) or conditioned or "non-cognitive" (e.g., influenced by patient's personal experience).

While evidence suggests that adjusting for treatment expectations may improve assay sensitivity, further work is necessary to determine the best approach to assess it in a reliable and valid way. For example, whether a single question is sufficient or whether more questions explicitly capturing cognitive and non-cognitive domains are necessary to adequately capture the concept of expectation (without inadvertently amplifying expectation with in-depth questioning) in the context of chronic pain trials warrants evaluation. Evaluation of potential measures of expectations that could be used as covariates in primary analyses to maximize assay sensitivity could be achieved through inclusion of different measurement tools using a SWAT ("studies within a trial")-like approach,[37] wherein participants are randomized within each arm of the study to complete one of two (or three) candidate expectation measures and their relative impact on assay sensitivity is evaluated.

In addition, delineating between treatment assignment expectations and outcome expectations and comparing which construct best predicts study outcomes may be worthwhile, considering our study suggests that the expectations for assignment to treatment or placebo groups may be overlooked when rating expectations. In fact, an interesting line of inquiry might focus on measuring expectations of study outcomes in general and separately measuring expectations supposing assignment to active treatment. This approach

would: (1) provide a clearer understanding of what drives ratings of overall expectations of study outcome and (2) allow for comparison of whether overall expectations or expectations specific to active treatment are most predictive of outcomes in a clinical trial. Such an investigation could be conducted systematically, again employing a SWAT-like approach, with randomization to rating overall expectations only or rating both overall expectations and expectations supposing active treatment.

It should also be acknowledged that outcome expectations are dynamic and may change over the course of a trial. If participants experience pain relief or adverse effects soon after initiating treatment, they may guess their assignment to active treatment (i.e., unblinding) and therefore recalibrate their outcome expectations accordingly. It should be noted, however, that participants' guesses are not always correct, as improvement and side-effects can occur independent of the treatment.[27, 32] In this dynamic context, outcome expectations might be viewed as a potential mediator of the effect of the intervention requiring more complex methods for analysis.

Outcome expectations may also change across the lifespan as a result of unique contextual and developmental factors. While there is a paucity of research devoted to this topic, it is of relevance given that different approaches to measurement may be necessary for pediatric and geriatric populations. For example, recent reviews suggest that children's expectations may be more easily modulated/impacted by suggestion compared to adults,[4, 35] and psychological determinants, such as magical thinking (which likely declines with age), is associated with larger placebo effects in children.[25] Further, while evidence of differential placebo effects by age is inconsistent,[33] given that developmental and/or degenerative processes can affect the endogenous pain modulatory system, the relationship between expectations and outcome may change across the lifespan. Perhaps most importantly, children and older adults are often part of a child-parent-clinician or patient-caregiver-clinician interaction. Given this complex psychosocial context, expectations may be influenced by a multitude of cognitive and non-cognitive factors. In fact, for clinical trials of chronic pain treatments among pediatric and geriatric populations, it may be useful to include measures of parents' or caregivers' expectations of outcome, respectively, in addition to the participants' expectations.

Importantly, aggregation of findings across multiple clinical trials that include valid baseline measures of expectation will permit an evidence-based conclusion about the potential moderating effect of expectations. These findings could then inform optimal study designs and statistical approaches for minimizing the impact of expectations on assay sensitivity in order to increase the ability of trials to identify true therapeutic effects of novel pain treatments. Worthwhile future directions may include: (1) identification and/or development of a measure(s) that is content-valid, reliably interpreted, and easily administered; (2) systematic evaluation and comparison of candidate measures embedded in clinical trials to select a measure that accounts for more variability in the primary outcome; (3) pre-specification of outcome expectations as a covariate in analyses of chronic pain RCT data, and; (4) aggregation of findings across studies to determine the impact of covariate adjustment on assay sensitivity. Given the notable challenges with analgesic drug development, including the discouraging observation of reduced effectiveness among

established pain therapies,[12, 13, 16] efforts aimed at improving assay sensitivity in clinical trials are critical in order to accelerate the identification of safe and effective therapies that might otherwise be overlooked. Assessing and adjusting for outcome expectations could be one effective strategy toward this important goal.

Declaration of Competing Interest

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Highlights

- Participants' outcome expectations may contribute to clinical trial outcome variability
- Outcome expectations are influenced by a number of factors
- A brief, content-valid measure of outcome expectations is needed
- Adjusting for expectations in clinical trial analyses may improve assay sensitivity

Figure 1.
Themes of contributions to expectations described participants