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Covariate adjustment in chronic pain trials: An oft-missed opportunity

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Abstract

Self-reported pain intensity, frequently used as an outcome in randomized clinical trials (RCTs) of chronic pain, is often highly variable and could be associated with multiple baseline factors. Thus, the assay sensitivity of pain trials (i.e., the ability of the trial to detect a true treatment effect) could be improved by including pre-specified baseline factors in the primary statistical model. The objective of this focus article was to characterize the baseline factors included in statistical analyses of chronic pain RCTs. Seventy-three RCTs published between 2016 and 2021 that investigated interventions for chronic pain were included. The majority of trials identified a single primary analysis (72.6%; n=53). Of these, 60.4% (n=32) included one or more covariates in the primary statistical model, most commonly baseline value of the primary outcome, study site, sex, and age. Only one of the trials reported information regarding associations between covariates and outcomes (i.e., information that could inform prioritization of covariates for pre-specification in future analyses). These findings demonstrate inconsistent use of covariates in the statistical models in chronic pain clinical trials. Pre-specified adjustment for baseline covariates that could increase precision, and assay sensitivity, should be considered in future clinical trials of chronic pain treatments.

Keywords

Covariate adjustment; randomized clinical trials; pain

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1. Introduction

Randomized clinical trials (RCTs) are considered the gold standard for evaluating treatment efficacy when appropriately designed, conducted, and reported.[8, 24] However, many aspects of trial design can affect the assay sensitivity of clinical trials (i.e., ability of the trial to detect a true treatment effect). In the context of clinical trials of pain treatments, maximizing the assay sensitivity is particularly important considering the generally subjective, and thus highly variable nature of the outcome (e.g., self-reported pain intensity), along with the decreasing effect sizes observed over the years for trials of drugs that have historically demonstrated efficacy.[9, 19, 50] One approach to increasing the assay sensitivity of RCTs is to adjust for baseline covariates in the primary analyses of trial outcomes. For example, a simulation study using trials in various therapeutic areas showed that adjustment for covariates that are at least moderately associated with outcomes increased the power of the clinical trials [32]. Of note, CONSORT guidelines [48] and regulatory agencies [16, 53] have recommended consideration of covariate adjustment in clinical trials.

Selecting covariates to include in RCT analyses should be based on evidence from prior studies or clinical observations regarding what factors are known, or expected to have strong or moderate associations with the primary outcome.[15] For pain trials, such baseline covariates may include demographic characteristics (e.g., age, sex, race), [6, 11, 18, 25, 28] pain characteristics (e.g., pain intensity, pain duration), psychological factors (e.g., anxiety, depression), [7, 41] or expectations of treatment outcome.[3] While randomization serves to balance groups with respect to baseline characteristics, for continuous outcomes, adjustment for covariates can improve precision and thereby increase assay sensitivity. Moreover, adjustment for a small number of covariates (relative to the sample size) that are not associated with the outcome does not generally have a substantial negative effect on power.[32] However, covariates should always be pre-specified in a primary analysis to prevent post hoc adjustments that could increase the chance of false positive conclusions, and should be reasonably limited to those that are likely to have strong or moderate associations with outcome.[48] Secondary or sensitivity analyses could be prespecified or post-hoc, especially if they are aimed to address imbalances in randomization and are clearly identified as post-hoc.[16] Reporting of such sensitivity analyses will contribute valuable information about which covariates are most likely to be correlated with outcome.

2. Understanding the landscape of covariate adjustment in recent chronic pain clinical trials: a review.

While adjustment for covariates may have positive implications for assay sensitivity, the prevalence of this practice and the types of covariates included in chronic pain RCT analyses have not been investigated. To that end, we reviewed RCTs published in major pain journals to determine the frequency of adjustment for different covariates in primary and secondary analyses of clinical trials of chronic pain treatments and whether sufficient information is being reported to inform the extent to which covariates are associated with outcomes to prioritize inclusion in primary analyses. In brief, we reviewed RCTs that reported efficacy for at least one experimental chronic pain treatment, were published between 2016 and

2021 in one of six major journals specifically focused on pain, and included greater than 50 participants per treatment group. Detailed methods for article selection, data extraction, and data analyses are described in supplementary eMethods.

A PRISMA flow diagram for article selection is displayed in the Supplemental Figure. After screening abstracts (N=2883) and full texts (N=322), we identified 73 articles for data extraction. Of the 946 items that were dual-extracted, there were 143 (15.1%) discrepancies; of these, 133 (93.0%) were due to an oversight by 1 of the coders and 10 (7.0%) were due to differences in interpretation.

The majority of trials had a parallel group design and the blinding level, intervention types, and included pain conditions were variable (e.g., chronic low back pain, osteoarthritis) (Supplemental Table 1). The average sample size per group was 113 (range = 50 – 366). Of the 73 included studies, 53 (72.6%) reported a single primary analysis (Table 1); the remaining studies reported multiple analyses of outcomes that they identified as primary or did not specify a primary analysis. The primary outcome was most commonly pain intensity (n=34, 64.2%) or pain/disease related disability or pain interference (n=8, 15.1%). Of these 53 studies that reported a single primary analysis, 32 (60.4%) adjusted for at least one covariate; 27 (50.1%) adjusted for the baseline value of the primary outcome, 11 (20.8%) adjusted for study site, 10 (18.9%) for sex or gender, 6 (11.3%) for age, and 2 (3.8%) for pain duration, concomitant medications, or baseline psychological variables. Fewer than 2% of studies adjusted for race or baseline body mass index (BMI). The median number of covariates included in those primary analyses that used adjustment was 2 (range 1–7, interquartile range = 1–3). Only 1 of these studies noted the significance of the association between specified covariates and the outcome and it did not report the magnitude of the association.[43]

Only 7 (13.2%) studies included a secondary analysis that used a similar statistical model as for the primary analysis, and either adjusted for additional (85.7%) covariates or removed covariates (14.3%). Of the 6 secondary analyses that added covariates, 16.7% added the baseline value of the primary outcome, or concomitant medications, 33.3% added sex/gender or age, and none added race or ethnicity. Five of these 6 analyses adjusted for other types of covariates such as primary pain diagnosis, renal impairment, or days per week with back pain (Table 1). One article reported secondary analyses that removed covariates that had been included in the primary analysis.

Given potential benefits and low risks of including a limited number of covariates in analyses of clinical trials,[32] it is surprising that only 60% of studies adjusted for any covariates in primary analyses of pain clinical trials. In particular, the fact that only 51% of studies adjusted for the baseline score of the primary outcome measure indicates an underutilization of covariate adjustment, considering it is well established that baseline symptom scores, including pain intensity, are highly correlated with endpoint scores in clinical trials.[5] Adjusting for covariates that are moderately to strongly associated with outcomes can increase power by accounting for a component of the variability in the outcomes. The magnitude of the treatment effect (“signal”) is thus judged against a smaller magnitude of its standard error (“noise”) after covariate adjustment. Our findings suggest

that covariate adjustment is potentially underutilized in chronic pain clinical trials. Below we discuss a non-exhaustive list of covariates that investigators could consider including in primary (or at least secondary) analyses. We also propose key information that should be reported to guide future analyses investigating which covariates are most useful for increasing precision of treatment estimates.

3. Covariates to consider for future chronic pain clinical trial analyses

Associations between baseline covariates and outcomes in clinical trials are rarely reported. Thus, the subsequent considerations are generally based on other types of evidence, including: (1) associations between a participant characteristic (i.e., covariate) and pain ratings or response to pain stimuli in cross-sectional studies; (2) differential treatment effects identified in subgroup analyses of clinical trial data and; (3) reports of treatment-by-subgroup interactions in analyses of clinical trial data. It is important to note that although such differences in effect sizes (i.e., based on descriptive subgroup analyses or treatment-by-subgroup interactions) suggest that a covariate is possibly associated with outcomes, this conclusion is not certain. For example, it could be that the treatment is beneficial in one subgroup but harmful in the other, in which case the overall association between the covariate and outcome is weak or absent. Thus, our recommendations are based on currently available evidence, and should be updated if reporting of the direct associations between baseline characteristics and outcomes is increased. Table 2 outlines potential covariates to consider for inclusion in future analyses.

3.1 Demographic characteristics

Multiple studies demonstrate that age, sex, race, and ethnicity are related to pain perception and modulation.[2, 6, 11, 12, 14, 18, 25, 36, 47] Meta-analyses or systematic reviews have investigated whether sex [44, 54] is associated with differential treatment response or identified age or sex as one or multiple predictors of pain treatment response; [29] however, we were unable to identify studies that systematically assess whether these demographic characteristics are associated with pain outcomes in clinical trials, irrespective of treatment assignment (i.e., information that is necessary to evaluate utility of including these covariates in trial analyses). Our findings indicate that data to inform such a systematic review would be limited because most authors do not report the magnitudes of covariate associations with outcomes in publications.

3.2 Baseline pain and other clinical characteristics

Baseline outcome measurements, including pain intensity, are often associated with endpoint measurements in clinical trials.[5, 49] Thus, inclusion of baseline pain intensity is highly recommended and consistent with our finding that baseline score of the primary outcome was the covariate most commonly included in the reviewed studies. It is important to note that the baseline score of the outcome variable should be included regardless of whether the outcome is the endpoint score or the change from baseline in the score.[4]

An association between baseline pain duration and outcomes in clinical trials of rheumatoid arthritis was reported in a metanalysis, indicating that longer pain duration at baseline was

associated with less change in outcomes.[1] However, it is likely that patients who have experienced pain for a shorter period of time are more likely to improve spontaneously over the course of a clinical trial and that baseline pain duration could be associated with pain outcomes, especially if a large proportion of participants in the trial have a relatively short history of pain (e.g., 3–6 months).[34] Variability of daily pain intensity ratings has been shown to be associated with treatment effects in clinical trials,[17, 30] and could be beneficial for inclusion in analyses of trials that use the mean of 7-day daily pain intensity ratings as the primary outcome.

Studies have identified an association between baseline psychological factors and the magnitude of pain response to opioids [31, 55, 58] and corticosteroid injections.[56] Affect has also been shown to be associated with experimental pain ratings in patients with chronic pain, further supporting the potential for baseline affect to be associated with pain outcomes in clinical trials.[13, 51] Thus, including baseline affect as a covariate in the statistical analysis could improve the precision of pain clinical trials.

Another covariate for consideration is physical function / physical activity. Self-reported vigorous physical activity has been found to be associated with increased descending pain modulation (reduced temporal summation of heat pain and higher conditioned pain modulation)[40]. Moreover, preoperative physical function (PROMIS-PF) has been associated with pre and postoperative (6-weeks and 3 months) neck and arm pain intensity among patients undergoing anterior cervical discectomy and fusion.[42] An overview of Cochrane reviews on physical activity and exercise for chronic pain in adults observed a modest effect of these interventions for treatment of chronic pain[23] and a follow-up meta-analysis focused on dose of intervention found a significant positive correlation of longer duration of physical activity/exercise and analgesia.[45] These findings highlight an important relationship between physical function / physical activity and pain and suggest that adjustment for these variables may be warranted.

3.3 Concomitant pain therapies

Concomitant medications, or continued use of current analgesics, is sometimes allowed in clinical trials in order to increase recruitment feasibility. Preliminary data suggest that allowing concomitant pain medications may decrease the difference between active and placebo groups in clinical trials.[10] To our knowledge, no studies have investigated the potential effects of concomitant non-pharmacologic treatments on effect sizes in pain clinical trials.[34, 35] Inclusion of concomitant treatments as covariates in secondary analyses and reporting of associations with outcomes might inform whether such covariates could be useful in primary analyses of clinical trials. Admittedly, generating variables related to concomitant use of analgesics and non-pharmacologic treatments is not simple. There are many different types of analgesics, with varying levels of efficacy for any given condition that are often used clinically at subtherapeutic dosages. There are also many types of non-pharmacologic treatments, whose efficacy can be greatly affected by fidelity to the intervention and frequency of use. How to define useful concomitant treatment covariates is an interesting topic for future research.

3.4 Expectations

Multiple studies have demonstrated a relationship between participants' baseline expectations and outcomes after treatment for chronic pain.[3, 22, 27, 38, 52, 57, 59] While there is some variability in these findings,[20, 21, 26, 33, 39] overall adjustment for baseline expectations could be beneficial for increasing the precision of estimates of treatment effects in clinical trials.[37]

4. Design and reporting practices regarding covariate adjustment

Pre-specification of covariates in the analysis plan is critical for ensuring the integrity of the trial results. Using statistical models to identify covariates with the strongest associations with outcomes or selection and presentation of the statistical models with the combination of covariates that provide the most favorable trial results (i.e., "cherry picking") can lead to bias in treatment effect estimates and increase the probability of a false positive result; this practice should be avoided,[16, 46, 48, 53] Therefore, explicitly reporting that covariates were "pre-specified" in publications would increase transparency.

Our review found that only 1 of the articles reported whether the association between covariates and trial outcomes was significant and this article did not report the magnitude of the association. This lack of reporting is an important missed opportunity to inform the research community regarding potentially useful covariates. Such reporting, at the very least in supplemental files, would allow for future systematic reviews to assess which covariates have the strongest associations with outcomes and best potential to improve assay sensitivity. This information would inform pre-specification of covariates for future chronic pain trials. It is important to note that associations between baseline covariates and outcomes are affected by other covariates that are included in a statistical model (e.g., covariates may be correlated with each other, affecting the association between each covariate and the outcome). This fact should be taken into consideration when interpreting results in systematic reviews if these data become more routinely reported. Finally, the associations of baseline characteristics with outcomes could be dependent on various factors including the study population and intervention (e.g., baseline activity level could be associated with outcomes in a trial evaluating a physical therapy intervention, but perhaps not in an analgesic drug trial).

5. Limitations of review methods

Several limitations of this review are worth noting. Our analyses were performed using clinical trials selected from 6 major pain journals and may not apply to RCTs published in other journals that target specific interventions (e.g., Neuromodulation) and diseases (e.g., Osteoarthritis and Cartilage, Cancer) or general medical journals. Articles reporting secondary analyses or RCT protocols were excluded. Therefore, we may have missed secondary analyses of RCT data that adjusted for covariates, but were published in subsequent papers. However, our goals were to elucidate whether investigators routinely adjusted for covariates in primary analyses and whether they reported sufficient information to determine whether the covariates were associated with outcomes. Due to variations in reporting, we were not able to evaluate definitively whether covariate adjustment was pre-

specified in the clinical trials. However, only one reviewed study indicated that adjustment was performed based on observation of baseline differences between groups. Our search was restricted to publications within the past 5 years. While it is possible that publications from the past 5 years do not provide a complete picture of trends for covariate adjustment in chronic pain clinical trials, our focus on more recent publications provides an overview of recent trends.

6. Conclusion

Adjustment for baseline covariates in analyses of clinical trials can improve precision and potentially increase assay sensitivity. Findings from our review suggest that covariates with demonstrated associations with pain outcomes are often not included in primary analyses of chronic pain RCTs and that few primary publications of pain RCTs report secondary analyses that adjust for different covariates. Increasing the frequency with which pre-specified covariates are included in primary analyses of pain RCTs could help speed development of novel pain treatments and decrease the chance of prematurely abandoning potentially efficacious treatments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Disclosures:

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Perspective:

This review demonstrates inconsistent inclusion and potential underutilization of covariate adjustment in analyses of chronic pain RCTs. This article highlights areas for possible improvement in design and reporting related to covariate adjustment to improve efficiency in future RCTs.

Table 1.

Covariate Adjustment (total number of studies = 73)

	N (%)
Single primary analysis specified	
Yes	53 (72.6)
No	20 (27.4)
Clinical trial registered (of 53 studies)	
Yes	49 (92.5)
No	4 (7.5)
Primary outcome (of 53 studies)	
Pain intensity	34 (64.2)
Pain and disease-related disability/pain interference	8 (15.1)
Disease-related health status/quality of life	5 (9.4)
Other (e.g., composite pain and adverse events, multiple)	6 (11.3)
Adjusted for covariates in primary analysis (of 53 studies)	
Yes	32 (60.4)
No	21 (39.6)
Covariates included in primary analyses	
Baseline value of primary outcome	27 (50.9)
Study site	11 (20.8)
Sex/gender	10 (18.9)
Age	6 (11.3)
Baseline psychological variable	2 (3.8)
Pain duration	2 (3.8)
Concomitant medications	2 (3.8)
Physical therapist	2 (3.8)
Geographical region (e.g., country, continent)	2 (3.8)
Race	1 (1.9)
BMI	1 (1.9)
Other *	7 (13.2)
Secondary analysis, using the same statistical model with added or removed covariates (of 53 studies)	
Yes	7 (13.2)
Added	6 (85.7)
Removed	1 (14.3)
No	46 (86.7)
Additional covariates included in secondary analyses (of 6 studies that added covariates)	
Baseline value of primary outcome	1 (16.7)
Sex	2 (33.3)
Age	2 (33.3)
Concomitant medications	1 (16.7)
Other **	5 (83.3)

Note, some frequencies may sum to >100% (e.g., simultaneous adjustment for multiple covariates)

* Current depression episode, baseline HbA1c level, constant vs. intermittent pain, sensory phenotype, parent-reported abdominal pain index score, living situation, study team

** Days per week of back pain, percent of back pain from back (vs. leg), healthcare utilization, time since last physical therapy, primary pain diagnosis, renal impairment

Table 2.

Potential covariates to be considered for adjustment in future trials

Covariate Domain	Covariates	Example of covariate measurement
Demographics	Age Sex / gender Race / ethnicity BMI	
Pain and other clinical characteristics	Baseline value of outcome measure (e.g., pain intensity, pain-related disability) Baseline pain duration Baseline pain variability Baseline psychological characteristics	Months/years with pain condition SD of baseline diary ratings[17] Depressive symptom (e.g., PHQ-9), anxiety (GAD-7), pain catastrophizing scale scores
Concomitant therapies	Concomitant pharmacologic treatments Concomitant non-pharmacologic treatments	Number of treatments, Dichotomous (yes/no) Number of treatments, Dichotomous (yes/no)
Expectations	Baseline expectations for treatment outcome	Credibility/Expectancy Questionnaire

Abbreviations: GAD-7: Generalized Anxiety Disorder scale; NRS = Numeric Rating Scale, PHQ-9: Patient Health Questionnaire; SD = Standard Deviation; SF-36 = Short-Form health survey; VAS = Visual Analog Scale; VRS = Verbal Rating Scale