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## NEUROPATHIC PAIN SECTION

# Predicting Treatment Response with Sensory Phenotyping in Post-Traumatic Neuropathic Pain

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## Abstract

**Objective**. Currently available treatments for neuropathic pain are only modestly efficacious when assessed in randomized clinical trials and work for only some patients in the clinic. Induced-pain or gain-of-function phenotypes have been shown to predict response to analgesics (vs placebos) in patients with neuropathic pain. However, the predictive value of these phenotypes has never been studied in post-traumatic neuropathic pain. **Methods**. Mixed-effects models for repeated measures were used to evaluate the efficacy of pregabalin vs placebo in subgroups with induced-pain phenotypes (i.e., hyperalgesia or allodynia) in data from a recent, multinational randomized clinical trial (N = 539) that identified phenotypic subgroups through the use of a structured clinical exam. **Results**. The difference in mean pain score between the active and placebo groups (i.e., delta) after 15 weeks of treatment for the subgroup with hyperalgesia was –0.76 ($P = 0.001$), compared with 0.19 ($P = 0.47$) for the subgroup that did not have hyperalgesia. The treatment-by-phenotype interaction, which tests whether subgroups have statistically different treatment responses, was significant ($P = 0.0067$). The delta for the subgroup with allodynia was –0.31 ($P = 0.22$), compared with –0.30 ($P = 0.22$) for the subgroup that did not have allodynia (treatment-by-phenotype interaction $P = 0.98$). **Conclusions**. These data suggest that hyperalgesia, but not allodynia, predicts response to pregabalin in patients with chronic post-traumatic neuropathic pain. This study extends the growing data supporting the utility of induced-pain phenotypes to predict response to analgesics in post-traumatic neuropathic pain. Sensory phenotyping in large, multisite trials through the use of a structured clinical exam has the potential to accelerate the development of new analgesics and improve the generalizability of clinical trial results.

**Key Words:** Phenotyping; Post-Traumatic Neuropathic Pain; Hyperalgesia; Clinical Trials

## Introduction

Currently available treatments for neuropathic pain are only modestly efficacious when assessed in randomized clinical trials [1] and provide relief for only a minority of patients in the clinic [2]. Neuropathic pain conditions are currently defined by etiology (e.g., neuropathy from diabetes or HIV). When classified this way, each condition includes patients with variable pain phenotypes or sensory profiles that are shared across the different pain conditions [3–5]. It is likely that these phenotypes are a manifestation of underlying pain mechanisms and thus that patients with similar phenotypes might respond better, and more consistently, to certain analgesic classes than others [6]. The ability to predict which patients are likely to respond to certain types of drugs would be beneficial for clinical practice and research. In practice, phenotyping could be used to prioritize the order in which patients with a specific neuropathic pain condition are offered available drugs, which could improve upon the current standard, a notoriously frustrating process of trial and error. In research, refining entry criteria to include patients who are likely to respond best would increase efficiency by improving the assay sensitivity of clinical trials within specific neuropathic pain indications, provide better information about the effect size of drugs for the subset of patients for whom they are likely to work best (i.e., inform personalized medicine), and guide generalizability between different neuropathic pain conditions based on phenotypic profiles.

The largest population of patients with chronic neuropathic pain seeking specialty care have nerve injury after surgery or another traumatic event (i.e., post-traumatic neuropathic pain [PTNP]) [7–9]. In these cases, the heterogeneity of the pain-inciting event (e.g., thermal injury from electrocautery, transection by a surgical instrument, or traction in the setting of an adjacent bone fracture) can compound the variability of pain mechanisms comprising this broadly categorized set of pain syndromes (e.g., post-mastectomy pain, post-herniorrhaphy pain). Thus, sensory phenotyping could be particularly useful to increase the precision of clinical practice and clinical trials of PTNP.

A handful of mostly small studies have suggested that sensory phenotypes, in particular induced-pain or gain-of-function phenotypes, can predict response to analgesics vs placebos in patients with neuropathic pain [6, 10, 11]. However, none of those studies have investigated the ability of phenotyping to predict treatment response in PTNP. Because of the decreasing prevalence of post-herpetic neuralgia, a neuropathic pain indication commonly used to evaluate new analgesics, and the growing burden of chronic, postsurgical neuropathic pain syndromes, the chronic PTNP population is increasingly used to assess the analgesic efficacy of neuropathic pain drugs [12–14]. Thus, a better understanding of differential response of phenotypic subgroups in this chronic pain population could increase the efficiency of drug development for neuropathic pain. The main goal of the present study was to investigate whether clinical exam-based identification of induced-pain phenotypes, similar to that found in previous studies, predicts response to pregabalin vs placebo in data from a large, international randomized clinical trial of PTNP.

## Methods

### Data Source

This study is a secondary analysis of de-identified data from an international, multicenter, placebo-controlled, randomized clinical trial of pregabalin for PTNP (ClinicalTrials.gov ID: NCT01701362) that was made available by Pfizer, Inc., and accessed through the secure Vivli online platform [11]. The present study was submitted to the University of Rochester Medical Center Research Subject Review Board. The Research Subject Review Board determined that the study was not research involving human subjects as defined by U.S. Department of Health and Human Services and U.S. Food and Drug Administration regulations. Therefore, Research Subject Review Board review and approval were not required, and informed consent was not obtained because of the exempt status of the study. The trial included patients with neuropathic pain (rated $\geq$4 out of 10 on a 0–10 numeric rating scale) after surgery or trauma lasting for at least 6 months. Potential participants were examined by a clinician who was trained in the use of a standardized, structured neurological exam for post-traumatic neuropathy to confirm that the pain location corresponded with the location of the surgery or injury and was associated with sensory signs (allodynia, sensory deficits) in the same neuroanatomically plausible distribution [15]. This structured clinical assessment was specifically designed to exclude confounding syndromes, such as localized nociceptive pain and complex regional pain syndrome. Participants were treated with pregabalin or placebo for a total of 15 weeks. The pregabalin dose was optimized in the first 3 weeks (150, 300, 450, or 600 mg/day), followed by a 12-week treatment period. The primary efficacy outcome of the trial was the 15-week mean of daily pain assessments made on a 0–10 numeric rating scale (0 = no pain, 10 = worst pain imaginable) that asked patients to "select the number that best describes your pain during the past 24 hours." More details related to the trial design can be found in the original publication [11].

### Phenotype Definitions

The sensory phenotypes examined in this analysis were obtained during the baseline screening visit. They included cause of pain (surgical or trauma), general induced pain (hyperalgesia or allodynia vs neither), hyperalgesia (presence vs absence), allodynia (presence vs absence), and nonpainful sensory symptoms (tingling or numbness/paresthesia vs neither). The presence or absence of hyperalgesia and allodynia was determined by the site investigators in the context of a structured neurological exam. Site investigators were trained in a standardized neurological assessment through live presentations and video training materials. These materials were informed by the grading system recommendations outlined in Treede et al. [16]. Study sites were provided with a standardized set of sensory mapping tools, which included a foam brush, safety pin, and tuning fork. Training included the precise application of each tool to the subject's skin. For example, training materials specified the number of skin strokes with the foam brush and the method for application of the tuning fork (stored at room temperature). The mapping protocol first identified the central point of neuropathic pain within the territory of the injured peripheral nerve, as specified by the patient during neurological examination. Subjects were asked to identify the region of maximal pain intensity and maximal sensory abnormality. These subject-identified sites served as the starting location for sensory testing. The presence or absence of sensory abnormality (e.g., hyperalgesia or allodynia) was determined by the site investigator on the basis of a comparison of subject responses to stimuli applied at the center of the painful area and in a reference area (i.e., outside of the neuroanatomic distribution of the injured peripheral nerve). The reference site for sensory testing was determined by the investigator on the basis of direct query of the individual research subject.

### Statistical Analyses

The primary aim of this study was to investigate whether, similar to previous studies in neuropathic pain, induced-pain phenotypes predicted response to pregabalin vs placebo in PTNP. The secondary aim was to investigate whether the presence of nonpainful sensory symptoms predicted the response. Descriptive statistics were used to characterize the percentage of participants with each phenotype. The mixed-effects model for repeated measures with an unstructured covariance matrix was used to evaluate the efficacy of pregabalin in each phenotypic subgroup, as well as the treatment-by-phenotype interaction, to evaluate whether differences in the effect size (i.e., differences in pain scores between groups) between phenotypic subgroups (e.g., those with and without hyperalgesia) were statistically significant. Each model included the baseline pain intensity (mean of daily baseline diary), country, trauma type (surgery vs other trauma), treatment (pregabalin vs placebo), the phenotype of interest, and the phenotype of interest–by–treatment interaction. Each phenotype of interest was assessed in a separate model. A $P$ value of 0.05 was considered significant for the interaction terms, and no multiple testing adjustment was made. Sensitivity analyses with multiple imputation to accommodate missing data were performed to test the robustness of the results and are presented in the Supplementary Data.

### Role of the Funding Source

The original trial was funded by Pfizer; however, Pfizer did not provide funds for the analyses presented in this article or have any input into the design or interpretation of these analyses. Pfizer was allowed to review the manuscript before submission but did not provide any input.

## Results

### Summary of Primary Trial Results

The primary results of the original trial have been published previously [11]. In brief, 539 participants were randomized and received treatment; 85% (233) and 80% (211) of the participants in the pregabalin and placebo groups, respectively, completed the trial. Participants were on average 53 years old, 49% had postsurgical pain, and the mean baseline pain score was 6.45 on the numeric rating scale. According to the previously reported analyses, the main effect of pregabalin on the total sample at the primary time point (15 weeks) was not significant (pregabalin vs placebo: –0.22 numeric rating scale points, $P = 0.18$). As a check to ensure the accuracy of the data in our hands, we analyzed the main treatment effect of the full sample at week 15. We obtained results similar to those presented in the original article (i.e., a small difference between groups in favor of pregabalin that was not statistically significant; mixed-effects model for repeated measures: –0.316, $P = 0.07$; multiple imputation: –0.242; $P = 0.17$). We also obtained results similar to those of a subgroup analysis performed in the original study that demonstrated a qualitatively larger effect size for the postsurgical pain subgroup than for the non–postsurgical pain subgroup. In the original report, the nominal $P$ value for the effect size of the postsurgical pain subgroup in a retrospective analysis did reach the conventional threshold of 0.05; however, in our analysis, it did not (pregabalin – placebo: surgical pain = –0.47, $P = 0.06$; nonsurgical pain = –0.16, $P = 0.51$; treatment-by-phenotype interaction: $P = 0.38$).

### Phenotypic Characteristics of the Study Sample

During the neurological examination, 346 (64%) participants were identified as having allodynia or hyperalgesia, with 297 (55%) having hyperalgesia and 280 (52%) having allodynia. Four hundred ninety-four (92%) participants reported having tingling or numbness/paresthesias.

**Table 1.** Distribution and overlap of sensory pain and trauma phenotypes

| | Hyperalgesia absent | Hyperalgesia present | | Tingling or numbness/paresthesia absent | Tingling or numbness/paresthesia present |
|---|---|---|---|---|---|
| Nonsurgical | 115 | 155 | Nonsurgical | 18 | 254 |
| Surgical | 124 | 142 | Surgical | 26 | 240 |
| | Hyperalgesia absent | Hyperalgesia present | | Hyperalgesia absent | Hyperalgesia present |
| Tingling or numbness/paresthesia absent | 29 | 15 | Allodynia absent | 192 | 66 |
| Tingling or numbness/paresthesia present | 210 | 282 | Allodynia present | 47 | 231 |

*Note:* Phenotyping information for at least one of the variables in the tables were missing for between 1 and 3 participants, thus the total numbers do not always add to 539.

**Table 2.** Pregabalin effects by phenotypic subgroups

| | Estimate | Standard Error | *P* Value |
|---|---|---|---|
| **Induced-pain (hyperalgesia or allodynia) phenotype** | | | |
| Effect for induced pain–absent subgroup (n = 192) | 0.1164 | 0.2937 | 0.6918 |
| Effect for induced pain–present subgroup (n = 346) | –0.5832 | 0.2175 | **0.0073*** |
| Treatment–by–induced-pain phenotype interaction | –0.6996 | 0.3654 | 0.0555 |
| **Hyperalgesia phenotype** | | | |
| Effect for hyperalgesia-absent subgroup (n = 239) | 0.1882 | 0.2630 | 0.4743 |
| Effect for hyperalgesia-present subgroup (n = 297) | –0.7613 | 0.2320 | 0.0010* |
| Treatment–by–hyperalgesia phenotype interaction | –0.9495 | 0.3505 | **0.0067*** |
| **Allodynia phenotype** | | | |
| Effect for allodynia-absent subgroup (n = 259) | –0.3112 | 0.2541 | 0.2207 |
| Effect for allodynia-present subgroup (n = 280) | –0.3006 | 0.2429 | 0.2159 |
| Treatment–by–allodynia phenotype interaction | 0.0106 | 0.3514 | 0.9759 |
| **Nonpainful sensory symptoms phenotype*** | | | |
| Effect for nonpainful sensory symptoms–absent subgroup (n = 44) | –1.3596 | 0.6258 | **0.0298*** |
| Effect for nonpainful sensory symptoms–present subgroup (n = 494) | –0.2401 | 0.1823 | 0.1879 |
| Treatment–by–nonpainful sensory symptom phenotype interaction | 1.1196 | 0.6519 | 0.0859 |

*Nonpainful sensory phenotype defined as participant endorsing tingling or numbness/paresthesia.

All models include the following co-variables: country, baseline pain intensity, and trauma type.

Estimate for the effects= difference in pain scores between active and placebo groups at week 15 in the indicated subgroup. Estimate for the treatment-by-phenotype interaction= difference in treatment effects between phenotypes (i.e., the indicated subgroups) at week 15.

*P*-values less than 0.05 (bolded) were considered significant.

Table 1 illustrates the overlap among different phenotypes and pain etiologies.

## Phenotypic Predictors of Treatment Effect

Table 2 presents the treatment effect (i.e., delta in pain scores) between pregabalin and placebo at week 15 for the phenotypic subgroups for each of the models. A negative delta indicates that the pain was lower in the pregabalin group than in the placebo group. The table also includes, for each model, the treatment-by-phenotype interaction, which tests whether the effect sizes for the two phenotypic subgroups are statistically different from one another. The delta for the subgroup with the induced-pain phenotype (i.e., hyperalgesia or allodynia) was –0.58 ($P = 0.0073$), compared with 0.12 ($P = 0.69$) for the subgroup that did not have either hyperalgesia or allodynia. The *P* value for the treatment-by-phenotype interaction was at the boundary ($P = 0.055$). The delta for the subgroup with hyperalgesia was –0.76 ($P = 0.001$), compared with 0.19 ($P = 0.47$) for the subgroup that did not have hyperalgesia. The treatment-by-phenotype interaction was significant ($P = 0.0067$). The delta for the subgroup with allodynia was –0.31 ($P = 0.22$), compared with –0.30 ($P = 0.22$) for the subgroup that did not have allodynia (treatment-by-phenotype interaction $P = 0.98$). The delta for the small subgroup (n = 44) that did not report nonpainful sensory symptoms was –1.40 ($P = 0.03$), compared with –0.24 ($P = 0.19$) for the subgroup that did report nonpainful sensory symptoms. However, the treatment-by-phenotype interaction for this model did not reach significant significance ($P = 0.09$). The sensitivity analyses with multiple imputation produced similar results (Supplemental Data).

The subgroup with hyperalgesia reported a larger change from baseline with pregabalin treatment than did the subgroup without hyperalgesia. The change in the placebo group was fairly similar between the hyperalgesia-defined subgroups (Figure 1A). In contrast, the subgroup without nonpainful sensory symptoms

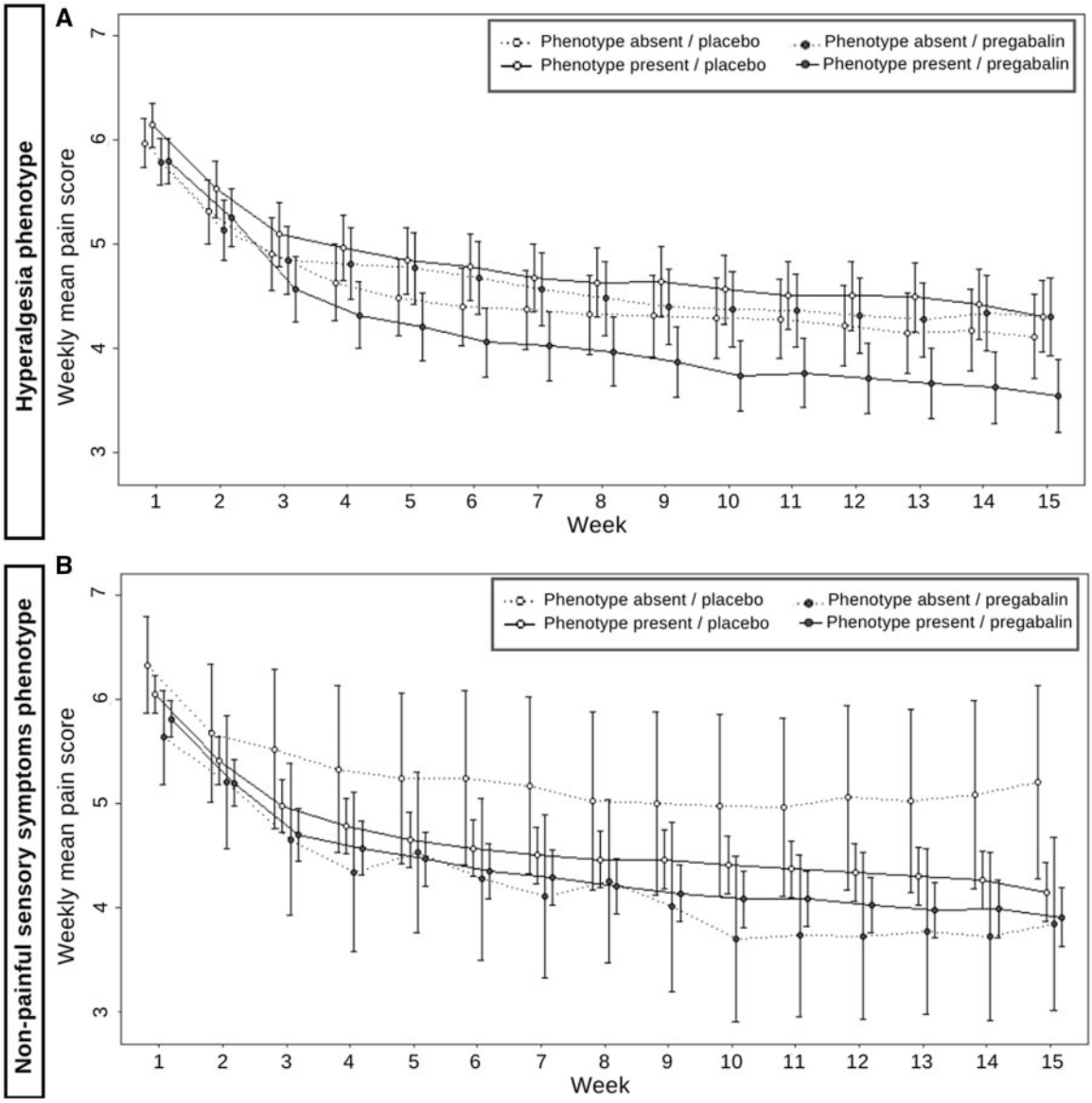


**Figure 1.** Trajectories of pain changes over within hyperalgesia- and nonpainful paresthesia–based phenotypic subgroups.

demonstrated a considerably smaller change from baseline in pain in the placebo group than did the subgroup that endorsed these symptoms, whereas the responses to pregabalin appeared to be fairly similar (Figure 1B).

## Discussion

To our knowledge, this is the first study to examine whether induced-pain phenotypes can predict response to treatment for chronic pain after peripheral nerve injury. The subset of participants presenting with hyperalgesia reported a larger benefit from pregabalin compared with placebo than did those without hyperalgesia. These results are consistent with smaller previous studies that suggested that sensory phenotyping can be used to predict treatment responses to oxcarbazepine, capscaicin, and pregabalin in other neuropathic pain conditions [10, 17–19]. Together, these studies suggest that regardless of the neuropathic pain etiology, sensory-based phenotypes might predict treatment response vs placebo response. They support the potential utility of these tools for targeted drug development by identifying sensory phenotypes that predict response to novel treatments in early-phase studies that could be used as enrichment-based entry criteria or stratification variables for future studies.

In our study, the allodynia phenotype did not predict response to pregabalin. These results are consistent with those presented by Simpson et al. [19], i.e., that mechanical and cold allodynia did not predict pregabalin efficacy in patients with HIV. These consistent results could be due to the fact that the studies both evaluated phenotypic predictors of the same drug, though in different conditions. Thus, whether hyperalgesia is a better predictor of treatment response than are more broadly defined

phenotypes of induced pain in other neuropathic pain drugs will require further investigation. One important difference between the Simpson et al. analysis [19] and ours was that they identified hyperalgesia as a pain rating of ≥8 out of 10 in response to pinprick, whereas the data we used were generated from a structured clinical exam. In their analysis, only 39 (13%) participants met the criteria for hyperalgesia. In our analysis 297 (52%) met the hyperalgesia criteria. Interestingly, the magnitude of the difference between pregabalin and placebo was larger for the hyperalgesia subgroup in their trial (2.14 points vs 0.76 points). The differences in both the size of the subgroups and the treatment effect size could be due to the Simpson et al. analysis [19] including more severe hyperalgesia than our analysis did. However, this hypothesis would need to be tested within the same sample. The differences between the results in these two studies highlight the importance of identifying phenotypic subgroups that will be sufficiently homogenous to identify participants likely to benefit most from the drug, but not so homogenous that participants who are likely to respond modestly to the drug are excluded. Although the inclusion of small, homogenous subgroups (e.g., severe hyperalgesia) could lead to large improvements in effect size and assay sensitivity, they would hinder recruitment and generalizability. One advantage of our study was that we showed that the subgroup identified as having hyperalgesia via clinical exam was half of the total sample in this large, international randomized clinical trial. Thus, this phenotype could improve assay sensitivity without greatly limiting recruitment and generalizability.

The cumulative evidence, including that from the present study, suggests that a sensory-based phenotype, likely related to hyperalgesia, can predict treatment response to multiple neuropathic pain drugs and in multiple neuropathic pain conditions. Thus, hyperalgesia could be a biomarker for a specific pain mechanism that is targeted by some of the currently available neuropathic pain drugs. Reverse translation of these findings could have implications for neuropathic pain drug discovery and development; however, the extent to which allodynia or hyperalgesia measured in animal models translates to an evoked pain phenotype in humans needs further validation with additional normative data for sensory profiling in rodents [20]. Our findings underscore the need for a collaborative research agenda that establishes definitive sensory profiles of new and existing rodent neuropathic pain models. In addition to the potential utility for reverse translation, these tools should be considered for future clinical trials, and they also potentially have utility in clinical decision-making. These results suggest that pregabalin might be particularly useful for patients who have neuropathic pain with hyperalgesia identified via standard neurological exam. This could help guide the order in which patients are offered currently available treatment options.

The second aim of the present study was to explore whether endorsement of abnormal, nonpainful sensations (e.g., tingling) would predict treatment response. The treatment effect was substantially larger in the subgroup of participants who did not endorse tingling or numbness/paresthesias (i.e., nonpainful sensory symptoms) (treatment delta = –1.36 vs –0.24); however, the treatment-by-phenotype interaction was not significant. This lack of interaction was potentially due to the small size of the subgroup without these sensations (n = 44), so these results should be explored in future studies. Interestingly, the larger treatment effect in this subgroup was due to a decrease in the placebo response and not to an increase in the response to pregabalin. If this difference is true and reproduced in future studies, it suggests that the presence of nonpainful sensory symptoms could increase the placebo response (or in other words, that the absence of nonpainful sensory symptoms could decrease the placebo response).

This study has some strengths and limitations. The strengths include that the data are from a large, international, multisite clinical trial, suggesting the feasibility of pain phenotyping in large confirmatory trials. The statistically rigorous treatment-by-phenotype interaction was pre-specified as the method to detect differences in treatment effect between phenotypic subgroups. The limitations include that although we had a general primary hypothesis that induced pain would predict response to treatment, we did not pre-specify hyperalgesia or allodynia as the primary analysis, and we did not adjust for multiple comparisons. Thus, these results should be interpreted as contributing to the growing body of evidence that suggests induced-pain phenotypes might be useful for predicting treatment response, and they should be interpreted as hypothesis generating with regard to evaluation methods. The method used to identify phenotypes was a standardized neurological exam rather than a quantitative sensory testing –based method. Although site investigators underwent video-based training on the standardized neurological exam, it was left to their discretion to determine whether a participant presented with hyperalgesia or allodynia (i.e., no specific cutoffs in pain induced by specific mechanisms were instituted). This is a weakness from a scientific perspective, but it does support the utility of less rigorous phenotyping methods in large clinical trials where the lengthy quantitative sensory testing exams are not possible. The simplicity of this phenotype would also increase the feasibility of phenotype-based clinical practice.

## Conclusions

This study is the first to extend the growing body of evidence suggesting that induced-pain phenotypes can predict response to analgesic treatment to chronic pain after peripheral nerve injury. Inclusion of pre-specified hypotheses with regard to phenotypic predictors of

treatment response (e.g., hyperalgesia and trauma type [surgical vs traumatic]) in future PTNP trials to confirm those identified in these analyses will help refine entry criteria to improve assay sensitivity for neuropathic analgesic drug development. These data would also inform clinical practice, specifically the order in which currently available drugs are offered to patients and the targeted generalizability of results across etiologically defined neuropathic pain conditions.

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## Data Sharing

De-identified data are available upon request to the sponsor via the Vivli platform. The data are not owned by the authors of this article, and thus, the authors do not have the right to share the data.

## Supplementary Data

Supplementary Data may be found online at http://painmedicine.oxfordjournals.org.

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