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Basal Heat Pain Thresholds Predict Opioid Analgesia in Patients with Postherpetic Neuralgia

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Background: **A variety of analgesics have been studied in the treatment of postherpetic neuralgia, with several medications demonstrating some degree of efficacy. However, existing trials have documented large individual differences in treatment responses, and it is important to identify patient characteristics that predict the analgesic effectiveness of particular interventions. Several animal studies have indicated that reduced basal nociceptive sensitivity, in the form of relatively high heat pain thresholds, is associated with greater opioid analgesia, but this finding has not been applied to human studies of opioid treatment for chronic pain.**

Methods: **Using data from a previously published crossover trial of opioids and tricyclics in postherpetic neuralgia, the authors evaluated baseline thermal pain thresholds, assessed at a body site contralateral to the affected area, as a predictor of treatment responses.**

Results: **During opioid treatment, a greater reduction in pain and higher ratings of pain relief were observed in patients with relatively higher heat pain thresholds at baseline. Baseline pain thresholds did not predict responses to tricyclics or placebo. Interestingly, other individual-difference variables such as age and baseline pain intensity also significantly predicted opioid responses (*i.e.*, higher baseline pain and younger age were related to greater opioid-associated pain reduction, with nearly 20% of the variance in opioid analgesia explained by these two factors).**

Conclusions: **These findings, which will require replication, suggest that pretreatment assessment of heat pain sensitivity might prove useful in identifying those patients most likely to respond to opioids.**

NUMEROUS medications, including opioids, tricyclic antidepressants, and anticonvulsants, have demonstrated efficacy in the management of neuropathic pain.[1] However, the best pharmacologic treatments often achieve a benefit of only 25–40% reduction in pain ratings for many chronic conditions, particularly persistent neuropathic pain.[1,2] Moreover, the wide variability in treatment outcomes makes it important to identify patient characteristics that are associated with better or worse outcomes for various interventions, with the eventual goal of tailoring pain treatments to individual patients.[3]

We and others have proposed that individual differences in basal pain sensitivity may be correlated with treatment outcomes.[4,5] For example, a growing animal literature suggests that mice with lower basal heat pain thresholds (*i.e.*, more heat pain–sensitive mice) evidence less analgesia in response to exogenous administration of opioids.[6–9] Correlations between baseline nociceptive thresholds and analgesic responses to morphine approach 0.7 in some studies,[6,10] indicating a potentially important, although poorly understood, association between individual differences in pain sensitivity and analgesia. Two human studies have partially replicated these animal findings, reporting that a higher tolerance for electrical pain at baseline was associated with greater morphine analgesia in an experimental pain model among healthy adults,[11] and that a higher presurgical tolerance for pressure pain was correlated with less postoperative morphine consumption after lower abdominal surgery.[12] To date, however, these findings have not been applied to clinical studies of humans with neuropathic pain.

A recent clinical trial[13] of opioids in patients with postherpetic neuralgia (PHN), a difficult-to-treat neuropathic pain syndrome, provided the opportunity to test this putative link between basal heat pain thresholds and opioid analgesia. PHN is characterized by spontaneous pain, as well as frequent evoked pains, with some patients demonstrating abnormalities in sensory responses in the zone of affected skin.[14,15] Opioids and several other classes of medications have shown efficacy in PHN,[1] although the average analgesic effect is modest. Previous analyses of the data from this trial[13] have suggested that the presence and nature of sensory alterations in the affected region may predict opioid responses; patients who show significant thermal hypoalgesia in affected skin, presumably as a result of C-fiber deafferentation, show less opioid analgesia than nonhypoalgesic patients.[16] Tella *et al.* have hypothesized that opioid responses are reduced in patients with significant deafferentation because the lost or injured C fibers bore major targets of opioid analgesics, μ-opioid receptors, which were presynaptic to these fibers' spinal synapses, the activation of which inhibited the release of nociceptive neurotransmitters.[16] However, no studies of PHN treatments have yet examined basal pain sensitivity in an unaffected area as a predictor of analgesic responses. Accordingly, we analyzed data from this randomized, placebo-controlled, crossover trial of opioids and tricyclic antidepressants (TCAs)[13] to examine whether baseline heat pain thresholds (HPThs), assessed

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at a body site contralateral to the PHN-affected area, predicted treatment responses.

Materials and Methods

Participants

Patients with PHN were recruited, *via* physician referrals and community advertisements, for a randomized, double-blind, placebo-controlled, crossover trial (see Raja *et al.*[13] for a full description of study methods and flow). Inclusion criteria included age older than 18 yr, no history of substance abuse, pain persisting for more than 3 months after resolution of skin lesions, and pain intensity ratings greater than 4 on a 0–10 numeric rating scale (see Raja *et al.*[13] for a complete description of study patients). A total of 76 patients were randomized; patients were 55% female, were largely white (88%), and had a mean age of 71 yr. All patients provided written informed consent; all of the study procedures were approved by the institutional review board (*i.e.*, Johns Hopkins Institutional Review Board, Baltimore, Maryland).

Trial Procedures

Upon randomization, all prescription medications for PHN were discontinued for at least 1 week, and then a 1-week drug-free baseline was completed. Pain ratings were collected by twice-weekly telephone calls during this period (*i.e.*, 0–10 rating scale, with 0 = no pain and 10 = most intense pain imaginable). Subsequently, subjects underwent, in random order, three treatment periods: one with an opioid, one with a TCA, and one with placebo. Each treatment period lasted approximately 8 weeks and had a titration, maintenance, and taper phase. The length of the titration period was flexible (generally 4 weeks); patients were started on 1 capsule per day at bedtime, and the dose was increased twice weekly. Starting doses were 15 mg MS Contin (morphine sulfate; Purdue, Norwalk, CT) in the opioid phase and 10 mg nortriptyline in the tricyclic phase; maximum daily doses were 240 mg MS Contin and 160 mg nortriptyline, taken in two or three divided doses. If intolerable side effects developed in patients taking two capsules or less per day, an alternative drug was used (*i.e.*, methadone in 5-mg capsules or desipramine in 10-mg capsules). Following a 2-week maintenance phase at the maximum tolerated dose, a 2- to 3-week taper was initiated. Treatment periods were separated by a 1-week, drug-free washout period. Pain intensity (0–10) and pain relief (0–100%, with 0 = no relief and 100 = complete relief) ratings were collected by twice-weekly telephone interviews made during the end of the maintenance period. Patients were informed that they could take over-the-counter analgesic medications during the study. Previous analyses indicated that there were no carry-over effects, and no correlation between pain reduction on opioids and pain reduction on TCA.[13]

HPTh Assessment

At baseline, HPTh was assessed bilaterally, at the affected site and the same mirror-image site, similar to previous studies[15] (see Discussion for an analysis of the limitations of this choice of testing location). The majority of randomized patients underwent HPTh assessment, although 12 of the 76 randomized patients were not tested before beginning treatment and thus could not be included in the current report. Contact heat stimuli were delivered using a Medoc Thermal Sensory Analyzer (TSA-2001; Medoc Advanced Medical Systems, Ramat Yishai, Israel). An ascending method of limits paradigm was used to assess pain thresholds; from a baseline of 30°C, the temperature of the thermode increased at 1°C/s until the subject responded, indicating that he or she "first felt pain," by pressing a button. Three trials of HPTh were performed on each side of the body, with the thermode repositioned between trials.

Statistical Analysis

A total of 64 patients, out of the original 76 randomized, underwent baseline HPTh assessment. As in the original report, we included data from all treatment periods in which patients took at least one dose of drug and gave pain ratings.[13] Of the 64 patients with HPTh data, 60 provided for at least one treatment period, 51 provided data for two treatments, and 40 provided data for all three treatments (see appendix). Of these 64, most (60.9%) had a thoracic or lumbosacral distribution of PHN, whereas 35.9% had a primarily trigeminal distribution. Two patients were affected primarily on the arm, and they were included in the thoracic/lumbosacral categorization. Only the HPTh data from the contralateral side were used in these analyses, because the previous studies all involved assessment of basal pain responses at an uninjured body site.

When using baseline HPTh as a predictor of treatment response, it was necessary to account for differences in sensitivity across body regions, because HPTh differs from site to site (*e.g.*, pain thresholds on the face are lower than thresholds on the back or chest).[17] Hence, we standardized patients' HPTh separately within the two anatomical regions (*i.e.*, thoracic/lumbosacral region *vs.* trigeminal region), yielding two distributions with a mean of 0 and an SD of 1 (*i.e.*, one for the thoracic/lumbosacral patients and one for the trigeminal patients). Patients could then be combined into a single group, without confounding individual differences in HPTh with differences in the location of HPTh assessment. For example, after standardization, a trigeminal patient with HPTh of 49.7 on the contralateral side and a thoracic patient with HPTh of 51.1 on the contralateral side would each have a standardized score of 1.0, reflecting the fact that each scored 1 SD above the mean within his or her distribution (see Results section for group means). We then used hierarchical linear regression to examine basal HPTh as a predictor of treatment re-

Table 1. Hierarchical Regression Predicting Percentage Change in Pain Intensity

	Opioid			Tricyclic			Placebo		
Step	Step R^2	F for Step	Standardized β	Step R^2	F for Step	Standardized β	Step R^2	F for Step	Standardized β
1									
Baseline pain	0.19	4.0†	−0.30†	0.09	1.4	−0.28*	0.26	4.9‡	−0.51‡
Age			0.29†			0.01			−0.09
Female sex			−0.12			0.08			0.01
2									
Contralateral HPTh	0.10	6.6†	−0.32†	0.00	0.2	−0.05	0.02	0.9	0.14
	$F(4,50) = 5.0$, $P = 0.002$, $R^2 = 0.29$			$F(4,45) = 1.1$, $P = 0.38$, $R^2 = 0.09$			$F(4,42) = 3.9$, $P = 0.01$, $R^2 = 0.28$		

Standardized βs are roughly equivalent to partial correlation coefficients for individual variables. The dependent variable, percentage change in pain intensity, is calculated such that lower values reflect greater pain reduction (*e.g.*, −100% indicates that pain intensity was reduced by 100%, reflecting complete analgesia). Therefore, the negative β for baseline pain indicates that higher baseline pain was associated with a larger percentage reduction in pain intensity, whereas the positive β for age indicates that older patients experienced less pain reduction than younger patients. Sex is coded as 1 = men, 2 = women.

* $P \leq 0.10$. † $P \leq 0.05$. ‡ $P \leq 0.01$.

HPTh = heat pain threshold.

sponse, measured in both terms of percentage pain reduction from pretreatment to maintenance and in terms of patient-estimated pain relief. We controlled for age and sex, because both of these factors can influence pain thresholds and treatment responses.[18,19] Finally, to enhance the clarity of presentation of the findings, we classified participants according to whether they had a good or a minimal response to opioids. Individuals with pain relief scores and percentage pain reduction scores of 30 or greater were classified as good responders, whereas those with pain relief and percentage pain reduction scores of less than 30 were classified as minimal responders[20]; these groups were then compared on baseline HPTh.

Results

Mean HPTh contralateral to the affected site was higher for patients tested in the thoracic or lumbosacral region relative to those with a trigeminal distribution (HPTh = 45.8 ± 5.3 for thoracic/lumbosacral patients, 43.9 ± 5.8 for trigeminal patients), although this difference did not achieve statistical significance ($P > 0.1$). Mean HPTh values at the affected site were similar for trigeminal patients (HPTh = 43.5 ± 5.5), whereas HPTh at the affected site for thoracic/lumbosacral patients was 48.0 ± 4.7. Standardized baseline HPTh scores were unrelated to patient dropout from the study or to the dose of opioid, TCA, or placebo that was achieved during the drug titration period, measured as the daily number of capsules taken during the maintenance phase ($P > 0.05$ for correlations between HPTh and the number of capsules within each treatment phase). Within the opioid phase, although some patients were taking MS Contin (15-mg capsules) and some were taking methadone (5-mg capsules), this 3:1 dose ratio is consistent with studies of equianalgesic opioid dosing within the range of doses used here.[21,22] In this trial, the mean maintenance dose of MS Contin was 91 mg (59% of patients); for methadone, the mean maintenance dose was 15 mg (41% of patients).[13] Standardized baseline HPTh scores were also unrelated to baseline PHN pain intensity e ($r = .01$).

In the regressions predicting pain intensity changes and pain relief with opioids, higher initial pain intensity was associated with a larger percentage reduction in pain. That is, the higher the pain was at baseline, the more it was reduced after opioid treatment. Notably, this effect did not vary as a function of the phase of the crossover trial in which a patient received opioids. Older age predicted less reduction in pain intensity and less pain relief after treatment with opioids (tables 1 and 2). Zero-order correlations of age with opioid-associated change in pain intensity and opioid-associated pain relief were $r = 0.31$ and $r = -0.32$, respectively (P values < 0.05). Sex approached significance as a predictor of pain relief, with women reporting marginally more pain relief than men during the opioid phase (mean for women = 48.7 ± 33.4, mean for men = 34.2, ± 29.6). HPTh on the unaffected side explained significant percentages of the variance in pain reduction (10%) and pain relief (18%), with higher baseline HPTh predicting larger reductions in pain and higher pain relief ratings (tables 1 and 2 and fig. 1).

The independent variables explained substantially less variance in responses to TCA, with no variables significantly predicting pain intensity change or pain relief after TCA treatment. Baseline pain intensity was a near-significant predictor, with a trend for higher baseline pain to correlate with greater treatment-associated reductions in pain intensity, as observed during opioid treatment. Similarly, only baseline pain intensity correlated with placebo-related changes in pain, an effect that did not vary according to the phase of the trial in which placebo was administered, and no variables significantly predicted placebo-associated pain relief.

Finally, we classified subjects as good responders or minimal responders according to their pain relief and

Table 2. Hierarchical Regression Predicting Pain Relief (0–100)

	Opioid			Tricyclic			Placebo		
Step	Step R^2	F for Step	Standardized β	Step R^2	F for Step	Standardized β	Step R^2	F for Step	Standardized β
1									
Baseline pain	0.17	2.9†	−0.09	0.02	0.3	−0.06	0.05	0.7	−0.05
Age			−0.33†			−0.10			−0.14
Female sex			0.25*			−0.07			0.16
2									
Contralateral HPTh	0.18	11.1‡	0.44‡	0.03	1.5	0.19	0.02	0.8	−0.16
	F(4,41) = 5.5, P = 0.001, R^2 = 0.35			F(4,41) = 0.6, P = 0.69, R^2 = 0.05			F(4,40) = 0.7, P = 0.60, R^2 = 0.07		

Sex is coded as 1 = men, 2 = women. A positive β therefore indicates that women tended to report more pain relief.

* $P \leq 0.10$. † $P \leq 0.05$. ‡ $P \leq 0.01$.

HPTh = heat pain threshold.

percentage pain reduction scores (*i.e.*, pain relief or percentage pain reduction scores ≥ 30, compared with those with scores < 30).[20] Subjects with percentage pain reduction scores of 30 or greater had higher HPTh (mean = 46.3, SD = 4.4) than those with percentage pain reduction scores of less than 30 (mean = 43.4, SD = 5.8; P = 0.04; for the comparison, see fig. 2). When this analysis was repeated using categorization of pain relief scores, a nonsignificant trend in the same direction was noted (P = 0.09; fig. 2).

Discussion

Quantitative sensory testing may be useful in illuminating patient characteristics that are associated with treatment outcomes.[4,5] Quantitative sensory testing has already become a valuable tool in the diagnosis of disorders such as fibromyalgia, the early identification of neuropathies,[23] the classification of sensory abnormalities in central pain,[24] and the subgrouping of patients.[25,26] The current results suggest that higher HPTH, assessed contralateral to the PHN-affected area, may possess some prognostic value in predicting a larger degree of analgesia from oral opioids.

The rather small sample size in the current study, the single measure of baseline heat pain responses, and the variety of anatomical sites assessed all necessitate replication of these findings in larger samples. Although this report is the first to focus specifically on the contribution of basal HPTh to opioid analgesia in PHN patients, other trials of opioids in PHN may also have collected quantitative sensory testing data that could likely be analyzed in similar ways. Moreover, it is especially interesting that the current findings achieved significance,

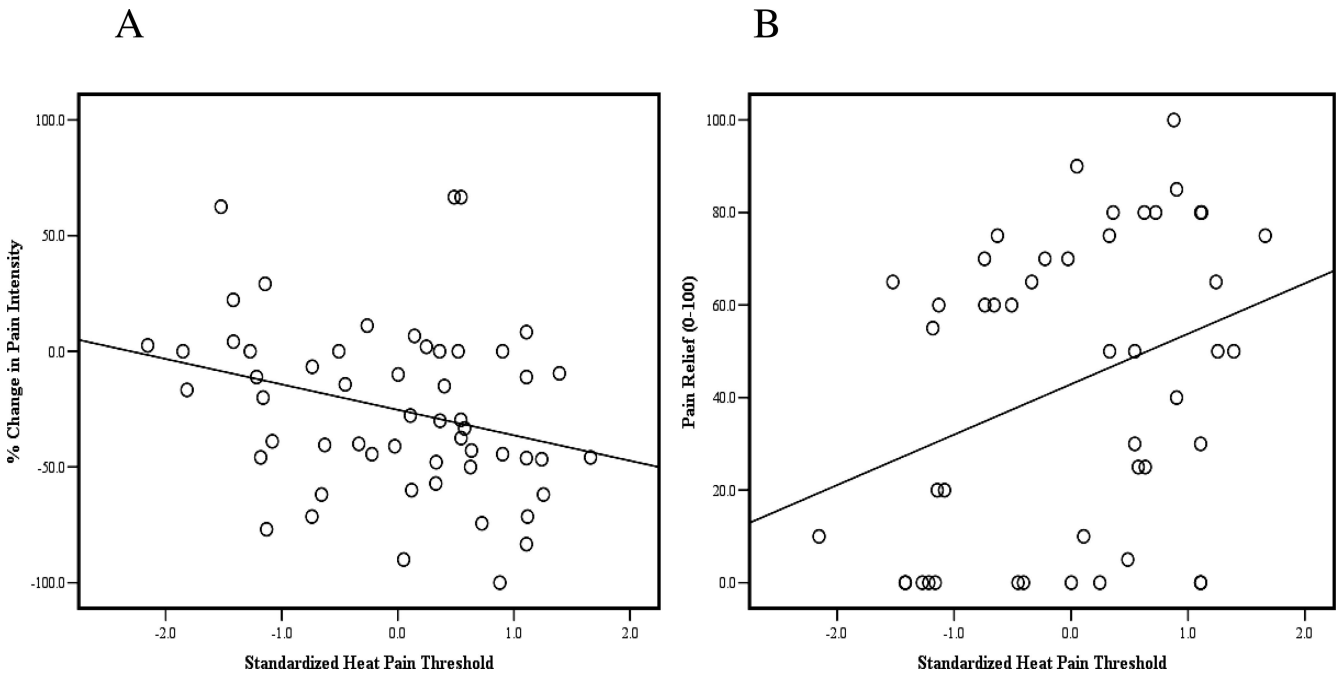

Fig. 1. Scatter plots of standardized baseline heat pain thresholds against percentage change in pain intensity (*A*) and pain relief scores (*B*) after opioid treatment.

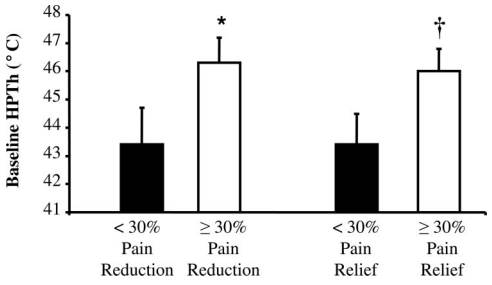

Fig. 2. Baseline heat pain threshold (HPTh) as a function of response to opioid treatment. Data are presented as raw means with SE bars. * $P < 0.05$ for the comparison of good responders with minimal responders. † $P < 0.10$ for the comparison of good responders with minimal responders.

given that HPTh was not measured at a consistent anatomic site for all participants. We should also note that the thresholds measured in the current study may not be equivalent to an individual's actual basal pain sensitivity, because previous work has suggested that unilateral PHN may be associated with bilateral peripheral nervous system changes in some patients, with homologous contralateral sites showing a substantial loss of epidermal neurites.[27] Therefore, replication of this work using distant body sites would be desirable. Interestingly, this effect should tend to work against the association we observed between HPTh and opioid effects, because greater contralateral neurite loss would presumably be correlated with both increased HPTh and with reduced opioid responses. Therefore, the current finding that higher HPTh predicts greater opioid analgesia may be a rather robust effect; future studies in this area may benefit from measurement of HPTh and other basal pain responses at a site remote from PHN-affected skin.

Individual differences in pain sensitivity are large, reflecting an amalgam of genetic and environmental factors that contribute to central and peripheral processing of pain.[28] For example, recent human genetic studies suggest that single nucleotide polymorphisms of specific genes, such as the μ-opioid receptor gene and the catechol-*O*-methyltransferase gene, are associated with basal pain sensitivity, with pain-induced μ-opioid receptor binding in the central nervous system, and with the development of chronic pain.[29–32] Although several previous studies have indicated that high baseline pain sensitivity is a risk factor for poor outcomes of multidisciplinary pain treatment,[33,34] this is, to our knowledge, the first study of individual differences in pain thresholds as predictors of analgesic responses to opioids in the context of chronic neuropathic pain. It is especially interesting to note that this association was specific to opioids, because basal HPTh did not influence treatment response to TCA or placebo.

Similarly, older age was associated with reduced treatment responses specifically to opioids, which may relate to either enhanced sensitivity of the very elderly to opioid side effects or age-related decrements in μ-opioid binding.[35,36] There was also a trend for women to report greater opioid-associated pain relief than men, consistent with some recent reports of sex differences in μ-opioid analgesia.[37] Finally, higher baseline pain intensity was generally related to larger reductions in pain across treatment types, including placebo. Because it was observed across treatments, this effect probably represents a regression to the mean phenomenon, such that those who begin treatment during an especially severe pain flare-up are most likely to report later reductions in pain, simply as a consequence of the natural variability in PHN pain. Previous reviews of statistical methods in clinical trials of pain treatments have indicated that use of baseline pain severity as a covariate in outcomes analyses often improves power, presumably because it accounts for variance in outcomes, similar to the effect we have observed here.[38]

Broadly speaking, the identification of factors that affect or predict responses to specific classes of analgesics has substantial implications for the design and powering of clinical trials. For example, the use of HPTh, age, or both as covariates in future trials of opioids for PHN pain, or the deliberate selection of younger and less pain-sensitive patients, could enhance the study power or reduce sample size requirements. However, these effects must be replicated in larger studies before such suggestions can confidently be offered. In these data, basal HPTH explained 10–18% of the variance in opioid analgesia, leaving room for other factors to explain still greater proportions of variance. Moreover, this study alone cannot serve as a basis for recommending an "HPTH screening test," and the sensitivity and specificity of such a procedure is unknown. To date, there is relatively little literature examining individual difference factors in opiate analgesia, although this represents an important area for pain researchers to explore.

Explanations for the findings that higher HPTh was associated with improved opioid analgesia may include shared genetic and/or neurophysiologic substrates regulating both basal pain sensitivity and responses to opioids,[6,10] with polymorphisms in the μ-opioid receptor gene being especially promising candidates.[39,40] Functional neuroimaging studies have also revealed that individual differences in basal responses to noxious thermal stimuli are reflected in differences in the activation of central nervous system pain-processing regions such as anterior cingulate cortex and prefrontal cortex,[41] which are rich in opioidergic neurons,[42] underscoring the possibility that a given brain network may participate in both thermal pain processing and opioid analgesic responses. A peripheral analgesic action of opioids in PHN (*i.e.*, direct inhibitory effects on primary afferents) is also possible,[13] however, and the current data cannot directly address the question of where in the nervous system the substrates for processing noxious heat may overlap with those contributing to opioid analgesia. Col-

lectively, the current study contributes to what we hope will be a growing literature on the prediction of individual differences in treatment outcomes for neuropathic pain, and further underscores the potential role of quantitative sensory testing in this line of investigation. Future PHN studies of other analgesics, such as the $\alpha 2$-δ calcium channel subunit modulators (*e.g.*, gabapentin[1,43]), may benefit from psychophysical assessment of pain thresholds as well.

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Appendix

Description of Patients Included in the Current Analyses

A total of 76 patients were randomized, and, of these, 64 completed heat pain threshold testing at baseline. Four of these 64 dropped out before receiving any drug treatment. Of the remaining 60 patients, 55 received at least one dose of opioid and provided subsequent pain ratings, 50 received at least one dose of tricyclic and provided subsequent pain ratings, and 47 received at least one dose of placebo and provided subsequent pain ratings. Overall, 40 patients provided data for all three treatments, and 51 provided data for two treatment periods (*e.g.*, with 45 providing data for both the opioid and tricyclic treatment periods).