Published in final edited form as:

Reg Anesth Pain Med. 2019 June ; 44(6): 660–668. doi:10.1136/rapm-2018-100196.

Response to BotulinumtoxinA in a Migraine Cohort with Multiple Comorbidities and Widespread Pain

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Abstract

Background—The Phase III REsearch Evaluating Migraine Prophylaxis Therapy (PREEMPT) protocol was developed in low risk migraine patients. We studied longitudinal response to treatment in a sequential retrospective observational cohort to evaluate predictors of effectiveness in patients with multiple overlapping pain syndromes treated in a quaternary pain management clinic.

Methods—We evaluated indicators of individual response in 402 consecutive chronic migraine patients who provided demographic information and used the Collaborative Health Outcomes Information Registry.

Results—The patients were middle aged 47 [38–56] median [interquartile range] years old and 83% women. They reported multiple complex pain problems with 11 [6–18] regions represented on a pain body map. Evaluated with NIH PROMIS measures, they reported higher scores for sleep impairment and disturbance, anxiety, depression, fatigue, pain behavior, pain interference and worse function and satisfaction with social roles compared to the general United States population; $P < 0.001$ for all domains. Within 120 days of treatment, 62% of patients reported reduced headache frequency. The best multivariable model developed for prediction of reduced headache frequency in response to treatment included lower treatment number, lower pain interference score, and less

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Conflicts of Interest:

The authors declare no conflicts of interest.

depression ($p=0.001$, 0.002 and 0.009). Depression may have been an obstacle to successful treatment; there was no association between depression score and number of treatments ($p = 0.54$).

Conclusions—Our findings point to the importance of identifying and addressing pain interference and depression and early in chronic migraine management and, more broadly, highlights the importance of multidisciplinary evaluation and treatment in chronic migraine.

Keywords

Migraine; Effectiveness Trial; PREEMPT; Risk Factors; Persistence of effect

Introduction

Prophylactic treatment with onabotulinumtoxinA for chronic migraine was approved by the United States Food and Drug Administration in 2010. Inclusion criteria for trials leading to drug registration are typically narrow. The phase III trials that led to the FDA approval included men and women with migraine headache meeting the International Classification of Headache Disorders criteria, ages 18 to 65 with headache at least 15 days per month at baseline lasting at least 4 hours.¹ Patients with complicated migraine, continuous migraine and those with medical complications that might be exacerbated by treatment with onabotulinumtoxinA, and those with elevated levels of depression (Beck Depression Index > 24) were specifically excluded from registration trials. Furthermore, patients were not allowed use of any migraine prophylactic medication within 28 days of starting the trials. Finally, patients with common comorbid pain disorders were also specifically excluded. While use of extensive exclusionary criteria is common practice in double-blind randomized trials designed to demonstrate that a treatment is effective, these relatively stringent criteria limit the generalizability of the results to complex pain patients with migraine who are treated in a real-world clinic setting. Comorbidity with other chronic pain disorders and use of multiple acute medications may create a subset of patients not evaluated in randomized trials who respond differently to treatment.^{2; 3}

To address this knowledge gap, we evaluated reduction in headache frequency in 402 consecutive chronic migraine patients treated with onabotulinumtoxinA according to the Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) protocol used for trial registration, at a single quaternary medical center pain management clinic.

The goal of our study was to identify predictors of effectiveness in medically in complex patients. We hypothesized that a subset of these complex patients could be identified such that those who are the most likely to benefit can be guided toward optimal multidisciplinary treatment. With this aim, we evaluated the associations between patient demographic, clinical, and treatment characteristics and the probability of positive response to treatment. Given that the current study was conducted within a pain management treatment setting, our outcome measures do not follow the traditional HIT-6 (Headache Impact Test) and MIDAS (Migraine Disability Assessment) outcome variables that are chiefly reported in headache literature and we cannot utilize pain diaries due to lack of patient adherence in a clinical setting. Instead, our measures constitute a comprehensive assessment of the wide impact of

pain on many facets of patients' lives, which has been proposed by national-level panels of pain experts as the optimal way to assess pain related outcomes in a comprehensive manner.⁴

Methods

We gathered data from 402 consecutive patients who had at least one follow-up visit after treatment with onabotulinumtoxinA at the Stanford Pain Management Center according to the protocol described in the PREEMPT studies between 10/30/2013 and 8/11/2016.¹ The starting date was that of the first patient treated with the PREEMPT protocol in our clinic (i.e., after FDA approval for chronic migraine). The final date was that when the current study was initiated. This study was approved by the Stanford University Institutional Review board on August 6, 2013 (IRB#28435).

Patients were identified using Current Procedural Technology codes for onabotulinumtoxinA injections associated with International Classification of Diseases-9 and -10 codes for chronic migraine. This is a convenience sample based on data available within the date range. The patients were evaluated by either a headache specialist or a pain medicine specialist and met the International Classification of Headache Diseases 3 beta criteria for Chronic Migraine. Moreover, to meet pre-requisites for insurance coverage for treatment with onabotulinumtoxinA, the majority had tried and failed 2–3 preventives treatments representing different drug classes. OnabotulinumtoxinA 155–195 U was administered as described in the PREEMPT protocol with 31 injections of 5 units to 7 head and neck muscle areas. Clinicians used the “follow the pain protocol” and administered an additional 40 units to head and neck areas that were particularly painful to the patient, as needed. This retrospective observational study of chronic migraineurs treated in a quaternary pain management center was designed to identify predictors of patients who would benefit from treatment with the PREEMPT protocol. Benefit was defined as patient reported reduction in headache frequency, the primary outcome used in registration trials.

Primary Outcome Variable

The primary outcome variable was patients' perception of whether headache frequency was reduced since their last clinic visit using a binary (“yes/no”) response. Specifically, patients were asked, “Since our last clinic visit, has there been a reduction in your headache frequency?”

In addition to the yes/no response described above, headache frequency after treatment was routinely collected by asking patients to select from an ordered polychotomous variable (1 = “less than 5 headache free days per month”, 2 = “5–9 headache free days per month”, 3 = “10–14 headache free days per month”, 4 = “15–20 headache free days per month”, and 5 = “Greater or equal to 20 headache free days per month”). This variable was used to assess the population response over time but was not assessed for association with predictive variables as pre- post- treatment values were not routinely available.

Assessment Variables

Demographic variables including, age, body mass index (BMI), gender, race, and ethnicity were recorded from clinical visit data. We assessed the complexity of the patients' pain

condition by evaluating overlap with other pain regions on a body map at each visit. The number of painful regions indicated on a body map was used as a measure of concomitant pain conditions. The National Institutes of Health PROMIS item banks evaluate domains of mental, physical and social health across multiple clinical conditions including pain and its management.^{5; 6} The values are normalized across the US population as t-distributions with a median at 50 and standard deviation of 10. A lower score represents less of the domain examined such that our cohort's median score of 40 for physical function (one standard deviation lower than that for the median US population score of 50) signifies poorer physical function compared to that reported by the US population as a whole. Mental health (General Health-mental sub-score, Anger, Depression and Anxiety), physical health (General Health-physical sub-score, Fatigue, Pain Behavior, Pain Interference, Physical Function, Sleep Disturbance), and social health (Satisfaction with Social Roles and Activities) were assessed with PROMIS instruments. Catastrophizing, described originally by Sullivan as, "an exaggerated negative mental set brought to bear during actual or anticipated painful experience" was measured with the Pain Catastrophizing Scale.⁷ This scale assesses domains of rumination, magnification of the negative consequences of pain, and helplessness related to pain that have been associated previously with enhanced physical and mental pain and response to treatment. The range is 0–52 with a cut off score of 30 (75th percentile) proposed as a cutoff for catastrophizing. As the Pain Catastrophizing Scale has not been scaled to an asymptomatic population, our cohort could not be compared to a normal distribution. Pain intensity was assessed over the previous 7 days using a 0–10 numerical rating scale (NRS).⁸

Data Collection

Data were collected using the Collaborative Health Outcomes Information Registry (CHOIR)^{9; 10} (<http://choir.stanford.edu>). CHOIR is an open-source learning health system that is integrated in the clinical care environment and allows for deep phenotyping of patients in a clinical setting. Data derived from CHOIR is used for point of care decision making, remote software based decision making, longitudinal characterization of patients and is a platform for research discovery. CHOIR is offered to all patients in the Stanford Pain Management Center and serves as a key component of new patient evaluation and follow-up evaluations. Five days prior to their scheduled appointment, patients receive an email with instructions to follow a web link to CHOIR and complete their patient survey. Patients who do not complete their CHOIR survey prior to their visit or lack the necessary technologies needed to access the survey (computer/smartphone, internet, email address) are asked to complete the surveys at clinic check-in using a tablet computer provided by the clinic. The number of data items available for each analysis is indicated in the representative figures. There were no other missing data unless indicated.

Statistical Analyses

To evaluate population trends, the polychotomous variable headache frequency per month was graphed (y axis) as a function of the number of days after the last treatment (X axis). The population trend was shown with a LOESS smoother with 99% confidence interval on the mean. The degree of improvement experienced by the population was quantified as the

percent of patients who transitioned from one level (e.g., less than 5 headache-free days per month) to another level (e.g., 10–14 headache-free days per month).

The primary outcome variable was each patient's reported reduction in headache frequency since the last clinic visit, (yes/no). This binary dependent variable was tested for association with the patient assessment variables (excluding polychotomous headache frequency) using logistic regression with the standard errors adjusted for clustering by patient. Analysis was restricted to responses that occurred within 120 days after treatment. A p value of less than 0.1 was required as screening for possible inclusion in the multivariable model. The multivariable model was built by sequentially testing each covariate that met the screening criteria, starting with the variable with the smallest p value. Once developed, covariates that had p-values greater than 0.01 were removed, starting with covariates with the lowest p values. The process assured that each covariate in the final multivariate model has $P < 0.01$. Treating $P < 0.01$ as statistically significant, and relying on 99% confidence intervals, was used in lieu of correction for the number of statistical comparisons in the multivariable logistic regression model. Interaction terms were assessed for all terms that remained in the final models, but all were $P > 0.16$ and were thus discarded. Each variable found to be significant with logistic regression was assessed for a threshold effect (i.e., violation of the assumption of linear logistic regression) by dividing the population into 5 quantiles and calculating fraction of positive responses in each. The observed proportion for each quantile was superimposed on the curve predicted by logistic regression, with the location on the x-axis being at the mean of the observations within the quantile. The impact of treatment number on the primary outcome variable was assessed with the Cochran Armitage Test for trend in proportions.

The statistical analyses were completed using R programming language version 3.3.2 accessed 12/31/2017 with ggplot2¹¹, car (Companion to Applied Regression)¹², and miceadds¹³ packages.

Results

Four hundred and two consecutive chronic migraineurs who were treated with onabotulinumtoxinA according to the PREEMPT protocol at Stanford Pain Management Center were evaluated. A demographic summary is provided in Table 1.

Baseline Patient Status

Among our patients, headache was complicated by other pain problems, as shown in Figure 1. All patients in our cohort reported comorbid pain in at least one body area in addition to the migraine related areas in the head and neck with 11 [6–18] (median [Interquartile Range (IQR)]) painful body map regions identified. Patients reported a baseline status of 25 [15–30] (median [IQR]) headache days per month with an average pain intensity reported as 6 [4–7] out of 10 (median [IQR]) in the 120 days preceding the first treatment. Five percent of patients admitted to being active smokers. Thirty-nine percent reported current use of alcoholic beverages. Seventy-six percent of patients reported treatment with an opioid at their initial visit and 38% at subsequent visits.

To inform their clinical care, patients were asked to complete a range of questionnaires at their visits that assessed physical, psychological and social functioning (see Assessment Variables). Figure 2 shows the details of the patient's responses to these questionnaires at their initial visit. Most of our patients were sleep impaired, anxious, and depressed. The average patient reported pain behavior, pain interference with poor physical function, and reduced satisfaction with social roles. Using one-group t-tests, each of these 6 scales was worse compared with the normalized US population ($P < 0.001$).

Treatment Details and Population Responses

Patients were treated with 1 to 10 injections of onabotulinumtoxinA, separated by a minimum of 3 months. Patients in our cohort had 3 [1–4] (median [IQR]) treatments. Figure 3 shows summary details regarding the number and timing of treatments and follow-up visits.

Figure 4a shows the number of headache free days per month following the last (most recent) treatment as an ordered polychotomous variable vs. days since treatment. As indicated above, the patients reported a baseline of 25 [15–30] median [IQR] headache days per month during the 120 days before treatment. The red line in Figure 4B shows the percent of patients who reported improvement from the worst category (<5 headache free days per month). Eighty-five days after treatment, approximately 32% of patients retained the worst status having less than 5 headache free days per month. The green line shows that approximately 18% of patients entered into the best category of >19 headache free days per month (i.e., that is required for acute treatment with triptans without risk of medication overuse headache after treatment).

The effectiveness of each treatment was the reduction in headache frequency, defined as a binary yes/no outcome. The effectiveness of each injection declined over the course of multiple treatments ($p < 0.0001$, Cochran Armitage Test for trend in proportions) with 42% of 160 patients reporting reduced headache frequency after the 1st treatment, 49% of 110 patients after the 2nd, 35% of 86 patients after the 3rd, 44% of 55 patients after the 4th, 32% of 62 patients after the 5th treatment, and 23% of 52 patients after the 6th, 30% of 30 patients after the 7th and 13% of 23 patients after the 8th treatment. The intervals between treatments were highly variable as shown in figure 3. There may have been a modest differences in the treatment intervals between those who reported improvement (153 [78,277] days) and those who did not report improvement (191 [90, 326]) (Wilcoxon test, $p = 0.015$; median difference -23 days, 95% Hodges-Lehmann CI = -46 to -4 days).

Primary Outcome Variable

Figure 5A shows that approximately 46% of patients reported reduction in headache frequency at 85 days after treatment.

Table 2 shows the univariate analyses demonstrating association of treatment response ("has there been a reduction in your headache frequency since your last visit?") with demographic, treatment, and psychological variables. One developed multivariable model consisted of treatment number and pain interference ($P < 0.0006$ and 0.002) as predictors of response. Treatment number and pain interference were uncorrelated (Pearson $r = 0.07$, $p = 0.25$).

Figure 5B show the decreasing probability of response with increasing treatment number adjusted for the pain interference score set its median among patients of 62. Figure 5c shows the reduced probability of response with increasing pain interference score adjusted for the treatment number set at its median among patients of 3. However, pain interference cannot be treated directly, and depression was collinear (Pearson correlation = 0.37) with pain interference. Another multivariable model was essentially interchangeable with the same area under the receiver operating characteristic curve to 4 significant digits. This alternative model included treatment number ($p = 0.0002$) and PROMIS depression score ($p = 0.009$). Treatment number and depression score were uncorrelated (Pearson $r = 0.05$, $p = 0.45$). Figure 5d shows the effect of PROMIS depression score adjusted for the treatment number fixed at its median among patients of 3.

Discussion

We report response of 402 consecutive chronic headache patients who received treatment with onabotulinumtoxinA according to the PREEMPT protocol for chronic migraine using a protocolized data collection system (CHOIR) developed to support clinical care. Our population sample comprised complex patients whom reported multiple pain areas in addition to their migraine, as typically treated in a quaternary care center. According to NIH PROMIS score, our average patient reported more sleep impairment and disturbance, anxiety, depression, fatigue, pain behavior, pain interference, poorer physical function and less satisfaction in social roles normalized to a broad sampling of the US population. This represents a population excluded from previous PREEMPT studies.

The PROMIS measures were developed by the NIH as a way of standardizing the physical, psychological and social health experience of individuals across a huge population (in this case, entire United States). Despite their potential utility, the PROMIS measures have not been frequently applied to migraine studies. The association of elevated distress and dysfunction shown in our PROMIS scores is consistent with prior studies, discussed below.

Our findings suggest that medically-complex migraine patients may be particularly resistant to treatment with onabotulinumtoxinA while it is difficult to directly compare results due to differences in outcome measures. Registration trials required exclusion factors that are very common on patients attending our clinic as discussed previously. Patients with complex migraine, neuromuscular disease, use of prophylactic medication, fibromyalgia, depression and other psychiatric disorders were specifically not included. In PREEMPT1 the difference in headache days was 7.8 with all patients starting at a median of 20 headache days per month.¹ In PREEMPT 2, patients reported 19.9 headache days in the baseline period and 10 days after treatment.¹⁴

Our patients were also less responsive to treatment compared to smaller studies of patients treated in a specialized headache clinic. Negro et al. reported that the proportion of patients with severe disease (HIT-6 score ≥ 60) decreased by 81% compared to 68% of our cohort that improved from the worst status.¹⁵ Another difference is that Negro found continual improvement from the 1st to 8th treatment. We did not find improvement with additional treatment, in fact the improvement significantly declined. Aydinlar's cohort had a lower

headache frequency at baseline with median 18 headaches per month that was reduced to 7 headaches per month by the 5th treatment.¹⁶ They did not find a monotonic decrease with repeated treatment. In a larger prospective study from the Hull Migraine Clinic, headache days were reduced from 27 to 18 and migraine days from 15 to 7.¹⁷

Treatment number had a negative relationship with response, however it was fairly stable until treatment number 4. Our cohort is perhaps unusual in that patients had up to 10 treatments in which the last quintile having 6 treatments the response dropped. In studies discussed above, treatment response increased¹⁵ or did not change.¹⁶

We evaluated associations between PROMIS variables and response to treatment to identify potential treatments that could impact effectiveness in future prospective trials. A multivariable model included treatment number and PROMIS Pain Interference score. Pain interference measures the consequences of pain on aspects of the patient's social, cognitive, emotional, physical and recreational activities. Low pain interference score might be used to favor early treatment with onabotulinumtoxinA. An interchangeable model consisted of treatment number and PROMIS Depression score. Unlike pain interference, a consequence of the pain that cannot be easily modified, depression is treatable with psychological therapy, medication-based intervention, and other non-pharmacological interventions (e.g., exercise).¹⁸ Consequently, our findings highlight the potential importance of effective pretreatment screening and planning, as well as the use of multidisciplinary approaches in chronic migraine, particularly those that address comorbid mood disturbance.

The relationship between chronic migraine headache and depression as an outcome variable has been evaluated in multiple previous studies, but few have evaluated depression directly as a predictor of response to treatment.^{16; 19–25} Consistent with our results, Maasumi found that the previous or current use of antidepressant medication (potentially a proxy for a diagnosis of depression) was a negative predictor of response to treatment with onabotulinumtoxinA.

While we found that higher PROMIS depression score was predictive of poor response to treatment, we found no association between treatment number and depression score suggesting that repeated treatment does not impact depression score (supplemental figure1). With respect association between migraine treatment and depression, Aydinlar and colleagues measured negative emotional states including depression, anxiety and stress with the Depression Anxiety and Stress Scales-21 questionnaire and did not find a reduction in this score associated with successful treatment.¹⁶ Concordant with our findings, Lin and colleagues studied 94 patients with chronic migraine and found only 40% improvement with treatment and no association with age or depression measured with Beck Depression Inventory score.¹⁹ Improvement in headache severity has been associated with improvement in depression.²⁰ The majority of the studies that found reduced depression after treatment were small open label studies of 17–60 patients treated for chronic migraine with onabotulinumtoxinA. A reduction in chronic migraine days was associated with decreases in depression according to the Beck Depression Inventory-II.^{21; 23; 24} Given that depression emerged as a salient predictor of poor treatment response in our cohort, it may be more appropriate to consider mood disturbance as a complicating factor that should be

addressed as part of PREEMPT protocols, as opposed to a comorbidity likely to improve after treatment administration.

Our patient population differs from that of a typical headache clinic. However, it has been shown that migraine, especially chronic migraine, is commonly co-morbid with many other diseases.²⁶ In a mail survey sent to over 46,000 Danish twins 62% of migraineurs had “neck trouble” and 70% had “low back trouble.”²⁷ In a cross-sectional survey looking at comorbid disease in fibromyalgia patients, 56% met criteria for migraine.²⁶ To specifically evaluate differences between chronic migraine sufferers from episodic migraineurs, Buse analyzed data from 24,000 headache sufferers in the 2005 American Migraine Prevalence and Prevention Survey. Concordant with our findings, they reported that pain and psychiatric disorder were more common in chronic than episodic migraine with 30% of chronic migraine patients reporting depression as measured by the PHQ-9 compared with 17% of patients diagnosed with episodic migraine. Similarly, 32% of chronic migraine patients had other chronic pain disorders as compared to 15% of episodic patients.²⁸ The association between chronic migraine and other pain disorders was again identified in an analysis of the Chronic Migraine Epidemiology and Outcomes study (CAMEO), a prospective web based study. Twenty-two percent of all pain conditions queried were associated with chronic migraine.²⁹

Ours is the largest outcome study of outcome using PREEMPT protocol based on routinely collected clinical data (as opposed to industry-funded registration studies).^{15; 17; 21; 30–34} Our CHOIR protocol did not include headache diaries, which we believe is an unrealistic expectation in routine clinical care. The PROMIS data allowed us to characterize our population based on psychosocial indicators of health and function in addition to their pain data. Like all retrospective studies, our data are not as complete and specific as those from prospective observational trials that use study specific instruments such as assessment diaries. While diaries are helpful for better recall, they are not practical in our clinical setting. The potential for recall bias must be considered, but is a necessary trade-off to gather treatment outcomes in the complex, real-world population of patients with chronic migraine, other chronic pain conditions, and comorbidities who are typically who may not participate in clinical trials.

Selection bias in prospective trials can be reduced by offering incentives to patients to return for follow-up assessment. Data gathered in the course of routine care are only available from patients who chose to present for care, introducing selection bias. Our findings are limited to patients who both chose to return for follow-up evaluation were willing to complete CHOIR follow-up visits, and did not capture patient data between clinic visits. Another key issue is sparse baseline data immediately prior to treatment, limiting per-subject per-treatment pre-post outcome comparisons. Nevertheless, the time course for change in treatment response was similar between the population analysis shown in figure 4 and the analysis of individual change shown in figure 5a. This work adds to a relatively limited body of literature demonstrating clinical effectiveness in complex patient populations with chronic high levels of medical and psychiatric comorbidity.

Complex pain patients with chronic migraine have frequent but incomplete treatment response to onabotulinumtoxinA administered according to the PREEMPT protocol. Predictors of positive response including treatment number, lower PROMIS pain interference and depression score may help set patient and provider expectations. These findings also underscore the importance of multimodal treatment in chronic migraine.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding:

Intradepartmental, NIH K24DA029262 (SM), Redlich Pain Research Endowment (SM), T32DA035165 (JS)

Abbreviations:

PREEMPT	The Phase III REsearch Evaluating Migraine Prophylaxis Therapy
HIT-6	Headache Impact Test
MIDAS	Migraine Disability Assessment
BMI	body mass index
CHOIR	Collaborative Health Outcomes Information Registry
IQR	Interquartile Range
CAMEO	Chronic Migraine Epidemiology and Outcomes study

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Figure 1. Body map Regions:

Percent of patients who reported pain within individual body regions with head and posterior neck regions indicated in red. Eighty-two percent of patients provided these data.

Figure 2: Responses to Questionnaires at Initial Visit

Box and whisker plots: bold black vertical line represents population median, box edges are 25th and 75th percentiles, whiskers are 95th percentiles, and green boxes are outliers. The vertical line at a score of 50 demonstrates the US population median for the NIH PROMIS scores. The units of the Y axis are 1/10th of a standard deviation (e.g., 1 standard deviation = 10 units). A higher NIH PROMIS score represents increased attribute. A higher score on a positive attribute, such as “Physical Function”, implies better health. A higher score on a negative attribute, such as Depression, suggests worse health.

The last attribute, Pain Catastrophizing, is not an NIH PROMIS score. The range is 0 to 52. Pain Catastrophizing is not normalized to a t distribution.

NIH PROMIS- National Institutes of Health (Patient-Reported Outcomes Measurement Information System) N- number of patients in this study who provided data

Figure 3: Population Treatment Details:

Four hundred and two patients had up to 10 treatments with onabotumlinum toxin A using the PREEMPT protocol. The box and whiskers plot depicts the treatment number on the x-axis and number of days since the first treatment on the y-axis. The number of patients who received each treatment appears in red text. The number of observations between treatments is indicated in black within the box. Treatment 0 shows the data collected prior to the first treatment.

Figure 4: Headache Free Days Per Month After Treatment

A. 293 observations of 186 patients within 120 days of treatment

Black bars are patient reports of headache days / month as an ordered polychotomous variable. The blue line is a loess smoother for all treatment responses/time and the grey shaded area is the 99% confidence interval for the smoother. The maximum population response is reached at 86 days after treatment.

B. The red line shows percent of patients improving from the worst category (fewer than 5 headache free days per month). The pale red shaded area shows the 99% confidence band of the predicted loess line, calculated using the R package ggplot2. The estimated percentage is 32% at 87 days after treatment. The green line shows percent of patients improving to the best category (20 or more headache free days per month) is increased to 18 (0–48) % with a plateau approximately 35 days after treatment after treatment. The pale green shaded area shows the 99% confidence band. The interruption is due to inability to calculate the 99% confidence band at these time points due to data sparsity.

Figure 5: Probability of Reduced Headache Frequency Since Treatment

Patients were asked the question, “Has your headache frequency improved since your last visit?”

A. All patient responses within one year of treatment. Red bars (at 0 on the y-axis) represent improvement since last visit and blue bars (at 1 on the y-axis) represent lack of improvement. The blue line is a loess smoother representing the probability of positive responses/time and the grey shaded area is the 99% confidence band for the smoother.

B. Logistic regression curves for negative association between treatment number and reduced headache frequency since the last visit, treatment occurring within 120 days, with $P < 0.0006$. Red and blue plus signs are raw data with jitter function applied to the x-axis to indicate sample size. Red plusses (at 0) represent no improvement since last visit. Blue plusses (at 1) represent improvement. Black dots represent the fraction of patients in 5 quantiles showing improvement. The black line is the predicted probability of benefit calculated from the logit line $e(\text{logit_line})/(1+e(\text{logit_line}))$ showing decreasing benefit with

increasing treatment number, while Pain interference score is fixed at its median value of 62 among all patients.

C. Logistic regression curves for negative association between pain interference and reduced headache frequency since the last visit, treatment occurring within 120 days with $P < 0.002$. Red and blue plus signs are raw data. Red plusses (at 0) represent no improvement from last visit. Blue plusses (at 1) represent improvement. Black dots represent the fraction of patients in 5 quantiles showing improvement. The black line is the predicted probability of benefit calculated from the logit line $e(\text{logit_line})/(1+e(\text{logit_line}))$ showing decreasing benefit with higher PROMIS Pain Interference score, while treatment number is fixed at its median number of 3 among all patients.

D. Logistic regression curves for negative association between depression and reduced headache frequency since the last visit, treatment occurring within 120 days with $P < 0.009$. Red and blue plus signs are raw data. Red plusses (at 0) represent no improvement. Blue plusses (at 1) represent improvement. Black dots represent the fraction of patients in 5 quantiles showing improvement. The black line is the predicted probability of benefit calculated from the logit line $e(\text{logit_line})/(1+e(\text{logit_line}))$ showing decreasing benefit with higher PROMIS Depression score, with treatment number fixed at its median among patients of 3 treatments.

Table 1

Demographic Variables describing the clinical cohort

Demographic variables						
	Asian	Black	Hawaiian	Other	White	Unknown
Race	13	6	1	79	201	102
	Non-Hispanic	Hispanic	Unknown			
Ethnicity	28	274	100			
	Female	Male	Unknown			
Gender	332	66	4			
	Median	IQR	Range	Unknown		
Age	47	38–56	16–102	0		
BMI	26	23–27	16–54	4		

. BMI, Body Mass Index kg/m²; BMI, Body Mass Index; IQR, Interquartile Range; IQR, Interquartile Range.

Table 2:

Univariate interaction between potential predictive factors and successful treatment.

	OR	99% CI	P*
Treatment Number	0.77	0.65–0.92	0.0002
PROMIS Pain Interference	0.93	0.89–0.99	0.0011
PROMIS Depression	0.95	0.90–0.99	0.0051
PROMIS Fatigue	0.96	0.92–1.00	0.0152
PROMIS Mental Health	1.05	1.00–1.12	0.0214
PROMIS Pain Behavior	0.93	0.84–1.04	0.0824
Hispanic Ethnicity	2.45	0.62–9.67	0.0929
PROMIS Satisfaction with Social Roles	1.03	0.98–1.03	0.1021
PROMIS Anxiety	0.97	0.93–1.01	0.1034
Pain Catastrophizing Score	0.99	0.96–1.02	0.3492
BMI	1.02	0.96–1.09	0.3754
Female Gender	1.65	0.38–7.17	0.3786
PROMIS Social Isolation	1.03	0.94–1.03	0.3900
Body Map Regions (number)	0.99	0.95–1.03	0.4288
Opioid Use	0.77	0.32–1.87	0.4523
PROMIS Physical Function	1.01	0.96–1.07	0.5827
PROMIS Physical Health	1.01	0.95–1.07	0.6501
PROMIS Anger	0.99	0.96–1.03	0.7176
Caucasian Race	1.13	0.35–3.67	0.7894
AGE	0.99	0.95–1.04	0.7918
PROMIS Sleep Disturbance	1.00	0.96–1.05	0.9541
PROMIS Sleep Impairment	0.00	0.00–1.00	0.9997

CI, confidence interval; OR, odds ratio; P*, P value.

Body Map (see figure 1).

* P value is for univariate analysis. BMI, Body Mass Index; CI, confidence interval; PROMIS, Patient-Reported Outcomes Measurement Information System.