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Original Article

Patients Receiving Integrative Medicine Effectiveness Registry (PRIMIER) of the BraveNet practice-based research network: Results of the chronic pain cohort

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ABSTRACT

Background: An increasing number of clinics are providing integrative medicine for chronic pain, creating a need for real-world, practice-based research. Our purpose was to conduct a multi-site prospective, practice-based, observational evaluation of patient reported outcomes in chronic pain patients.

Methods: This study took place at seventeen BraveNet Practice Based Research Network integrative medicine clinics. Chronic pain patients receiving personalized, integrative medicine interventions at BraveNet clinics were eligible. Participants completed the Patient Reported Outcomes Measurement Information System-29, Perceived Stress Scale-4, and the Patient Activation Measure at the index/baseline visit and at 2, 4, 6, and 12 months. Diagnostic and billing codes were extracted data from patients' health records. Linear mixed-model and multivariate analyses evaluated changes from index visit through 12 months.

Results: A total of 4883 patients enrolled, 3658 qualified and 967 of them endorsed chronic pain, completed at least two outcomes at 2 time points, had evaluable electronic health record data, and had at least one integrative medicine visit during the study period. Participants had a mean age of 51.6 years (SD 13.88) and were mostly white (81.8 %), female (78.3 %), educated (≥ college degree: 70.1 %). Significant improvements were observed on all 7 Patient Reported Outcomes Measurement Information System subscales, Perceived Stress Scale, and Patient Activation Measure scores at 12 months.

Conclusions: Chronic pain patients receiving care at integrative medicine clinics reported significant improvement over time in multiple domains of pain and quality of life. Future research with more sites and a common set of outcomes would further guide clinical practice.

Trial Registration: Clinical Trials.gov NCT01754038

1. Introduction

According to the 2019 National Health Interview Survey (NHIS), chronic pain impacts 20.4 % or roughly 50 million US adults, with women and adults over 65 years old reporting the highest prevalence.[1] Using multi-year data from the Medical Expenditure Panel Survey, US adults reporting painful health condition(s) increased from 32.9 % (~120 million adults) in 1997/1998 to 41.0 % (~178 million adults) in 2013/20,14.[2] Regardless of the definition, in a report from 2010, chronic pain costs were estimated to range from $560 billion to $635

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billion and are expected to be much higher now.[3] Although a prevalent treatment for chronic pain in the US, opioid analgesics are often ineffective, have serious side effects, and can lead to tolerance, dependency, and overdose.[4,5] In 2016, the CDC published guidelines denoting that nonpharmacological therapies are preferred for chronic pain treatment[6] and in 2022 updated the guidelines for opioid prescribing for pain.[7] A recent, comprehensive review concluded that there is significant evidence supporting the efficacy of non-pharmacologic interventions for the treatment of chronic pain.[5]

Integrative medicine (IM) is an approach to medicine that provides patient-centered care and addresses the physical, emotional, mental, social, and spiritual aspects that may affect a person's health.[7] IM utilizes non-pharmacologic therapies to effectively treat chronic pain, which is by far the most common reason that patients seek care at IM clinics.[8-10] According to the results from a 2007 National Health Interview Survey (NHIS) with a focus on IM, 38 % of American adults reported using IM interventions for general health and approximately 25 % utilized these approaches for treating chronic pain (e.g., back, neck, joint, arthritis).[11]

Observational and effectiveness research is often conducted in practice-based research networks (PBRNs) which allow for clinicians/investigators at multiple clinics to use a standardized method and platform to combine their data and increase generalizability of results.[12] In contrast with research conducted in randomized trials, PBRNs collect data in routine clinical care, so results have high ecologic validity, i.e., results are more reflective of "real world" outcomes.[12] Because of the increasing number of clinics providing IM[13] and the resulting need for IM clinics to conduct real-world, practice-based research, BraveNet was created as the first national IM PBRN.[8] BraveNet is a registered PBRN with the Agency for Healthcare Research and Quality (AHRQ) (RoPR ID: 40) and at the time of this study it consisted of 17 IM clinics each with a strong clinical delivery of IM interventions, robust patient populations, and solid research capabilities. Prior BraveNet studies were cross-sectional and focused on the characteristics of individuals electing to receive care at IM clinics.[8] The notable exception was the SIMTAP study which included 252 chronic pain patients across 9 BraveNet clinics and reported mean decreases in the Brief Pain Inventory pain severity (−23 %) and interference (−28 %) at 24 weeks.[9]

Accordingly, Patients Receiving Integrative Medicine Interventions Effectiveness Registry (PRIMIER) was launched in 2013. PRIMIER was designed as a multi-site prospective, practice-based, observational study to include all types of patients seeking care at IM clinics within the BraveNet PBRN. As outlined in our study protocol[14] and overall patient cohort study,[15] PRIMIER used a common data collection platform with validated patient reported outcome (PRO) measures (Patient Reported Outcome Measurement Information System: PROMIS) to understand which IM interventions patients receive in real-world IM clinical encounters, and whether specific IM interventions improve patients' reported quality of life over time. In this article, we report results on PRO changes from PRIMIER patients presenting with chronic pain, the largest patient cohort within PRIMIER.

2. Methods

2.1. Study design

This was a prospective, longitudinal, observational evaluation of patient reported outcomes (PROs) for patients with chronic pain as part of the PRIMIER study.

2.2. Eligibility criteria

PRIMIER was open to any patient aged 18 years or older who was seen by an IM provider for any clinical purposes at any of the 17 BraveNet member clinics (listed in Supplemental Table 1) from August 2013 to October 2017. One-year follow-up assessments were complete by October 2018. Those who were involved only in an education program or expected one-time activity at time of enrollment were not eligible for study participation. Inclusion into the chronic pain cohort required participants to report their pain as 4 or greater on an 11-point numeric rating scale for greater than 3 months at the index (baseline) visit. Inclusion also required patients to have electronic health record (EHR) data with at least 1 IM visit with a clinic provider (e.g., physician, massage therapist, acupuncturist) from the index visit to 12 months.

2.3. Ethics

All participants provided electronic informed consent before initiation of any study-related procedures. They could provide informed consent via pen and paper, if computer access was an issue. The protocol was approved by the Institutional Review Board (IRB) at each participating site. The Duke University Health Systems (previous IRB) and the Einstein Human Research Protection Program (current IRB) approved the study as the BraveNet Data and Statistical Coordinating Center. The study is registered in Clinical Trials.gov (NCT01754038).

2.4. Enrollment

Potential participants received information about enrolling in PRIMIER either from clinic or research staff. Those who decided to participate in PRIMIER were asked to log onto the PRIMIER website and electronically enroll directly into the registry. Participants did not receive any financial remuneration for their participation.

2.5. Data collection

From August 2013 to May 2015, PRIMIER data were obtained using the Patient Reported Outcomes Measurement Information System (PROMIS) Assessment Center at Northwestern University. From May 2015 to October 2017, PROs were obtained via Research Electronic Data Capture (REDCap), a secure, web-based application to obtain data for research studies.[16] REDCap automates data export procedures to numerous statistical software packages (e.g., SPSS, SAS and STATA) (http://project-redcap.org). Participants received e-mail messages to complete the PRO measures at five time points: index and 2, 4, 6 and 12 months.

2.6. Demographics and patient-reported outcome (PRO) measures

Demographic measures obtained from the participant at the index visit included: age, race, ethnicity, sex, education, marital, employment and insurance status, likelihood of insurance billing, household income, self-reported height and weight, alcohol and tobacco use, nutrition and exercise habits, and use of opioid medications.

2.6.1. Primary and secondary outcome measures

The PROMIS-29 is a widely used and validated PRO with four-item subscales covering seven distinct constructs: anxiety, depression, fatigue, pain interference, sleep disturbance as well as physical function and satisfaction with social role (http://www.healthmeasures.net/explore-measurement-systems/promis). Participants are instructed to reflect on their status over the previous 7 days and respond on a 1–5 Likert Scale. PROMIS-29 scores are then centered and scaled to T-scores, with mean = 50 and SD = 10. The PROMIS-29 also contains a single item 0–10 numeric rating scale (NRS) for participants to rate their pain intensity. To provide a more global measure, the PROMIS-29 subscales are combined into an overall composite score and physical and mental health summary scores.[17,18] Our primary outcome was Pain Interference and out secondary outcomes were the other PROMIS-29 subscales and the Summary Scores.

2.6.2. Other outcome measures

Derived from the original 14-item scale, the Perceived Stress Scale - 4 item version (PSS-4) is a brief, validated and widely used measure[19] consisting of four questions to measure the degree to which participants perceive situations in their lives as stressful.[20,21] Participants are asked about perceived unpredictability, uncontrollability, and overload and choose responses from never (0) to very often (4) with a total score ranging from 0 to 16.

The Patient Activation Measure (PAM) is a brief, validated measure for assessing the knowledge, skills and confidence essential to managing one's own health.[22] The 13-item PAM results in a score between 0 and 100 and divides participants into one of four activation levels: Level 1 – Does not believe that he/she has an active or important role; Level 2 – Lacks confidence and knowledge to take action; Level 3 – Beginning to take action; and Level 4 – Maintaining behavior over time.[23] Each level addresses a broad array of self-care behaviors and offers insight into the characteristics that drive health activation.[23]

2.7. Utilization/Intervention data

We used two methods to assess each participant's IM utilization: 1) at each visit participants self-reported their prior use of IM therapies and type of IM provider, based on the National Health Interview survey[11]; and 2) electronic or paper medical record extraction of each participant's interactions with the IM clinic (e.g., dates of all appointments and IM services received). The EHR extractions also included diagnostic codes (International Classification of Diseases: ICD-9 or ICD-10) and billing codes (Current Procedural Terminology: CPT) associated with each visit. All protected health information was encrypted and sent electronically to the BraveNet data coordinating center. IM encounters provided in the clinic and charted in the EHR included: a visit with an integrative physician, nurse practitioner, psychologist, acupuncturist, massage therapist, health coach, chiropractor, physical therapist, energy therapist or mind/body therapist (yoga, tai chi, biofeedback, hypnosis, meditation).

2.8. Statistical analysis

2.8.1. General statistical considerations

Only participants who: (1) completed the index PRO assessment, (2) completed ≥1 follow-up PRO assessment, (3) had evaluable EHR data and (4) had ≥1 IM visit at a BraveNet clinic in the 12 months of their study participation were included in the statistical analyses and referred to as "Participants". Those who completed the index PRO assessment but did not complete any follow-up PRO assessments will be referred to as "Lost to follow-up". Since attrition is a common occurrence in real-world, practice-based research,[24] we conducted a post-hoc analysis to explore whether there were any demographic differences between the Participants and Lost to follow-up, using *t*-test for continuous variables or chi-square tests for categorical variables. We also performed a sensitivity analyses (see below) to address potential bias due to missing data due to loss to follow-up. There was no imputation for missing data. Counts and percentages are reported on categorical variables and continuous variables are reported as means and standard deviations (SDs) and/or medians (25th and 75th percentiles).

2.8.2. Tests of changes in outcomes

For each PRO, we tested whether there was change at 2, 4, 6, and/or 12-months by performing a paired *t*-test of the changes of the outcome measure between each time point and the index time. Then, we fit a linear mixed effect model using the outcome at each visit as the dependent variable, the time indicators for each visit (2, 4, 6, or 12-months) as the predictors of interest, the intercept (for the index visit), and the potential confounders of age and sex. The estimated mean changes from the index time at each of four visits and 95 percent confidence intervals (CI) were reported for twelve outcomes: PROMIS-29 sub-scales, Physical and Mental Health Summary scores, Composite scores, as well as the PSS-4 and PAM scores. We performed Wald tests with a conservative Bonferroni method to account for multiple comparisons (α=0.05/48=0.001). The correlation within repeated measures from the same subjects and same site were accounted for by the random intercepts.

2.8.3. Sensitivity analyses

A possible issue of missing data due to the loss of follow up was addressed by applying stabilized inverse probability weights to the linear mixed effects model for the primary outcome, PROMIS-29 Pain Interference score. Detailed description of the sensitivity analysis can be found in Dusek et al.[15]

2.8.4. Minimal clinical important differences

The minimal clinical important difference (MCID) is a valuable way for assessing whether statistically significant changes are clinically meaningful at the individual patient level. The MCID was calculated as $a \geq 3$ point improvement for individual patients on the primary outcome, PROMIS-29 Pain Interference and secondary outcomes, other PROMIS-29 subscales, the Mental Health and Physical Health Summary scores and the Composite score.[14] Patients who reach the MCID threshold at 2-, 4-, 6- or 12-month time points are referred to as "responders" for that survey.[22]

2.8.5. Index visit factors that affect the trend of pain reduction

The multivariable longitudinal linear mixed effects models were fit to test whether index visit factors affect the rate of pain reduction during the following year. The primary outcome variable was PROMIS pain interference measurements between index and 12 months (the visit date for those who made 12-months visits, and 365 days from index for those who did not). The candidate covariates were 15 index variables as main effects at index visit as well as interaction terms (i.e., change in slopes) with the time between index and each follow-up visit. The interaction terms, the parameters of interest, measure the effect of predictors on the pain reduction rate over time. The candidate index variables were employment status, education, insurance type, PAM score, race (white vs. non-white), BMI (categorical), self-reported IM use in prior 6 months, four PROMIS scales (anxiety, fatigue, sleep, depression), baseline PROMIS pain interference level (categorical), sex, age (categorical), and site. The last four variables were forced to be in the model, but other predictors were further selected by backward elimination using Akaike information criterion (AIC) as the criteria of model fit. Correlation due to repeated measures were accounted for by subject-specific random intercept.

3. Results

A total of 4883 patients enrolled in PRIMER at the 17 member sites from August 2013–October 2017 with 3658 meeting eligibility for analysis in the full PRIMIER cohort.[15] Of these, 1552 (42.4 %) affirmed that they had chronic pain (pain as ≥4 on 11-point NRS for 3 months or longer) at the time of the index visit. Of those, 967 (62.3 %) completed the index survey AND at least one of the follow-up surveys at 2, 4, 6 or 12 months, AND had evaluable EHR data, AND attended at least one IM session at one of the participating PRIMIER clinical sites. These patients were therefore included in the analyzed Chronic Pain cohort (see Fig. 1). As this was a multi-site study, enrollment varied across sites ranging from 9 to 194 participants (mean of 56.9), largely based on the differing size of the clinics and when the sites started their participation in PRIMIER (See Supplemental Table S1). The number of subjects completing follow-up surveys were: 2 months (n = 724), 4 months (n = 602), 6 months (n = 519) or 12 months (n = 620). For the primary outcome (PROMIS Pain Interference), missing data on the primary outcome averaged 19.5 % and was just 3.5 % at the 2-month follow-up.

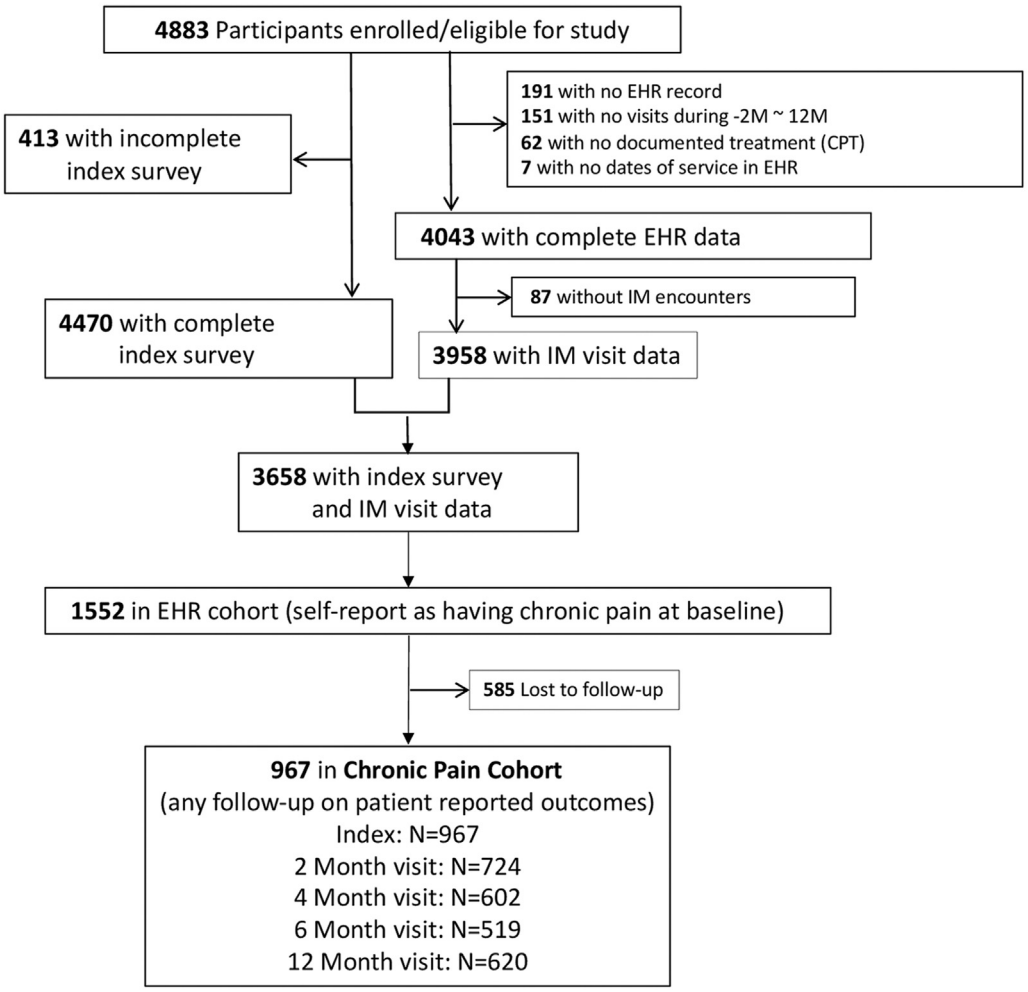

Fig. 1. CONSORT Diagram.
Abbreviations: CPT, Current Procedural Terminology; EHR, Electronic Medical Record; IM, Integrative Medicine.

3.1. Demographics and patient-reported outcome (PRO) measures

Table 1 displays the demographic characteristics of the 967 chronic pain PRIMIER participants included in the statistical analyses compared to the 585 participants who did not complete any follow-up assessments ("Lost to follow-up"). There were some differences between the groups on age, education, self-reported IM experience in 6 months, opioid use and PROMIS subscales and the PSS and PAM measures. For those in the chronic pain cohort (n = 967) the mean age was 51.6 (13.9 SD), most were White (81.8 %), female (78.3 %), and well educated with 70.1 % reporting a college degree or beyond (see Table 1). Average scores on the PROMIS-29 Pain Interference (61.9), Fatigue (59.0), Anxiety (56.4) and Physical Functioning (42.0), and the PSS-4 (6.3) for those in the chronic pain cohort were elevated (+/- 0.5 SD) relative to national norms.

3.2. Utilization/intervention data

A heterogeneous mix of pain diagnoses were charted in EHR at patients' index visit: pain in any location (43.6 %), lower back pain (17.2 %), myalgia (11.3 %), sciatica (7.5 %), arthritis (5.2 %), and chronic headache (5 %). Relevant other diagnoses or disorders were sleep disorder (4.2 %), anxiety (3.8 %), and depressive disorder (3.4 %). Multiple EHR pain conditions per participant were possible.

As shown in Table 2, over the 12-month study, participants experienced numerous IM interventions in the BraveNet clinics. From the index visit to 2 months, 82.2 % of participants received at least one IM service with the most common being medical doctor (MD)/nurse practitioner (NP) consult (46.3 %), acupuncture (32.7 %), and manual therapies excluding chiropractic (e.g., osteopathic manipulation, massage, physical therapy; 14.2 %) (see Table 2). Over the entire 12-month study period, 62.4 % of patients received at least one MD/NP consult, 42.3 % received acupuncture, and 24.2 % received manual therapies.

3.3. Changes in patient reported outcomes

3.3.1. Unadjusted results

Unadjusted changes in the primary outcome, PROMIS-29 Pain Interference and select PROMIS-29 sub-scales, Mental Health and Physical Health Summary Scores and Composite Score, PSS, and PAM scores from index to 2, 4, 6, and 12 months are displayed in Fig. 2. The unadjusted means, standard deviations, and medians for PRO scores over time are provided in the Supplemental Table S2 with statistical significance assessed via paired t-tests. This analysis revealed significant improvements at 12 months ($p < 0.001$) on all 7 PROMIS-29 subscales, Mental Health and Physical Health Summary scores, Composite score and the PSS-4 and PAM. Pain Interference, fatigue, social activation, pain intensity, Mental Health Summary score, Physical Health Summary score, and the Composite score were significantly improved at all 4-follow-up timepoints ($p < 0.001$).

Table 1
Demographics characteristics and patient reported outcomes at index for participants and lost to follow-up.

Characteristic or outcome	Participants (n = 967)	Lost to follow-up (n = 585)	P-value
Age (Years), *Mean (SD)*	51.60 (13.88)	48.81 (13.75)	0.0001
Sex			0.6302
Female	753/962 (78.3 %)	451/584 (77.2 %)	
Male	209/962 (21.7 %)	133/584 (22.8 %)	
Race			0.1442
White	775/947 (81.8 %)	471/571 (82.5 %)	
Black/African American	87/947 (9.2 %)	41/571 (7.2 %)	
Asian	17/947 (1.8 %)	19/571 (3.3 %)	
Other	68/947 (7.2 %)	40/571 (7.0 %)	
Ethnicity, Hispanic Latinx	76/ 934 (8.1 %)	55/569 (9.7 %)	0.3080
BMI, *Mean (SD)*	28.07 (6.81)	28.60 (7.30)	0.1528
Self-reported IM use in prior 6 months	823/952 (86.4 %)	451/579 (77.9 %)	<0.0001
Current tobacco use	63/952 (6.6 %)	59/571 (10.3 %)	0.0097
Education			0.1153
College degree	323/963 (33.5 %)	192/583 (32.9 %)	
Graduate/professional degree	352/963 (36.6 %)	185/583 (31.7 %)	
Employment			0.0103
Working full-time	336/956 (35.1 %)	221/583 (37.9 %)	
Retired	160/956 (16.7 %)	68/583 (11.7 %)	
Medical leave; Disabled	173/956 (18.1 %)	138/583 (23.7 %)	
Income			0.0202
< $20,000	169/918 (18.4 %)	111/579 (19.2 %)	
$20,000 – 50,000	191/918 (20.8 %)	147/579 (25.4 %)	
$50,001 - $100,000	258/918 (28.1 %)	135/579 (23.3 %)	
$100,001 - $150,000	136/918 (14.8 %)	68/579 (11.7 %)	
> $150,000	134/918 (14.6 %)	86/579 (14.9 %)	
Primary Health Insurance			0.3032
Medicare/Medicaid	304/957 (31.8 %)	167/581 (28.7 %)	
Private	639/957 (66.8 %)	407/581 (70.1 %)	
Plan to bill insurance (n = 1306)	531/768 (69.1 %)	237/340 (69.7 %)	0.2368
Opioid prescription (n = 1208)	127/682 (18.6 %)	123/422 (29.1 %)	0.0159
Self-reported first visit (n = 1357)	338/704 (48.0 %)	287/457 (62.8 %)	<0.0001
PROMIS Summary Scores			
Mental Health Summary score[@]	41.93 (7.56)	39.58 (8.03)	<0.0001
Physical Health Summary score[@]	41.21 (7.92)	39.78 (8.75)	0.0018
Composite score[#]	57.0 (6.50)	59.2 (6.90)	<0.0001
PROMIS subscales			
PROMIS Anxiety[#]	56.36 (9.13)	58.67 (9.35)	<0.0001
PROMIS Depression[#]	53.44 (9.13)	55.71 (9.83)	<0.0001
PROMIS Fatigue[#]	58.99 (10.00)	60.86 (10.43)	0.0006
PROMIS Sleep Disturbance[#]	54.27 (8.11)	56.19 (7.98)	<0.0001
PROMIS Pain Interference[#]	61.94 (7.79)	63.94 (8.05)	<0.0001
PROMIS Social Role[@]	45.20 (8.27)	43.43 (8.72)	<0.0001
PROMIS Physical Function[@]	41.96 (7.91)	40.86 (8.76)	0.0131
PROMIS Pain Intensity[#] (0* - 10)	5.59 (1.91)	6.07 (1.94)	<0.0001
PROMIS Global QOL[@]	2.95 (1.01)	2.70 (1.05)	<0.0001
Perceived Stress Scale[#]	6.32 (3.48)	7.06 (3.56)	<0.0001
Patient Activation Measure, Mean (SD)	64.14 (15.92)	61.87 (17.07)	0.0083
Levels			0.0019
Level 1: Starting to take a role	145/962 (15.1 %)	129/578 (22.3 %)	
Level 2: Building knowledge and confidence	144/962 (15.0 %)	90/578 (15.6 %)	
Level 3: Taking action	248/962 (25.8 %)	143/578 (24.7 %)	
Level 4: Maintaining behaviors	425/962 (44.2 %)	216/578 (37.4 %)	

Abbreviations: BMI, body mass index; IM, integrative medicine; PROMIS, Patient-Reported Outcomes Measurement Information System; QOL, quality of life; SD, standard deviation.
[@] Mean scores should increase if patient improves;.
[#] Mean scores should decrease if patient improves.

Table 2
Number and percentage of patients that had IM therapy encounters across time. IM Interventions extracted from EHR during the 12-month timeframe (n = 967).

	Index – 2 months	2 - 4 months	4 - 6 months	6 - 12 months	Index - 12 months
Consult MD/NP	448 (46.3 %)	322 (33.3 %)	249 (25.7 %)	326 (33.7 %)	603 (62.4 %)
Acupuncture	316 (32.7 %)	210 (21.7 %)	164 (17.0 %)	193 (20.0 %)	409 (42.3 %)
Manual	137 (14.2 %)	106 (11.0 %)	107 (11.1 %)	134 (13.9 %)	234 (24.2 %)
Mind/body	98 (10.1 %)	69 (7.1 %)	47 (4.9 %)	54 (5.6 %)	142 (14.7 %)
Chiropractic	72 (7.4 %)	55 (5.7 %)	51 (5.3 %)	59 (6.1 %)	111 (11.5 %)
Consult coaching	39 (4.0 %)	21 (2.2 %)	24 (2.5 %)	27 (2.8 %)	66 (6.8 %)
Energy therapy	10 (1.0 %)	10 (1.0 %)	10 (1.0 %)	19 (2.0 %)	25 (2.6 %)
Other	3 (0.3 %)	2 (0.2 %)	3 (0.3 %)	12 (1.2 %)	14 (1.4 %)
Any IM therapy	795 (82.2 %)	567 (58.6 %)	442 (45.7 %)	535 (55.3 %)	967 (100 %)

Abbreviations: EHR, electronic health record; IM, integrative medicine; MD, medical doctor; NP, nurse practitioner.

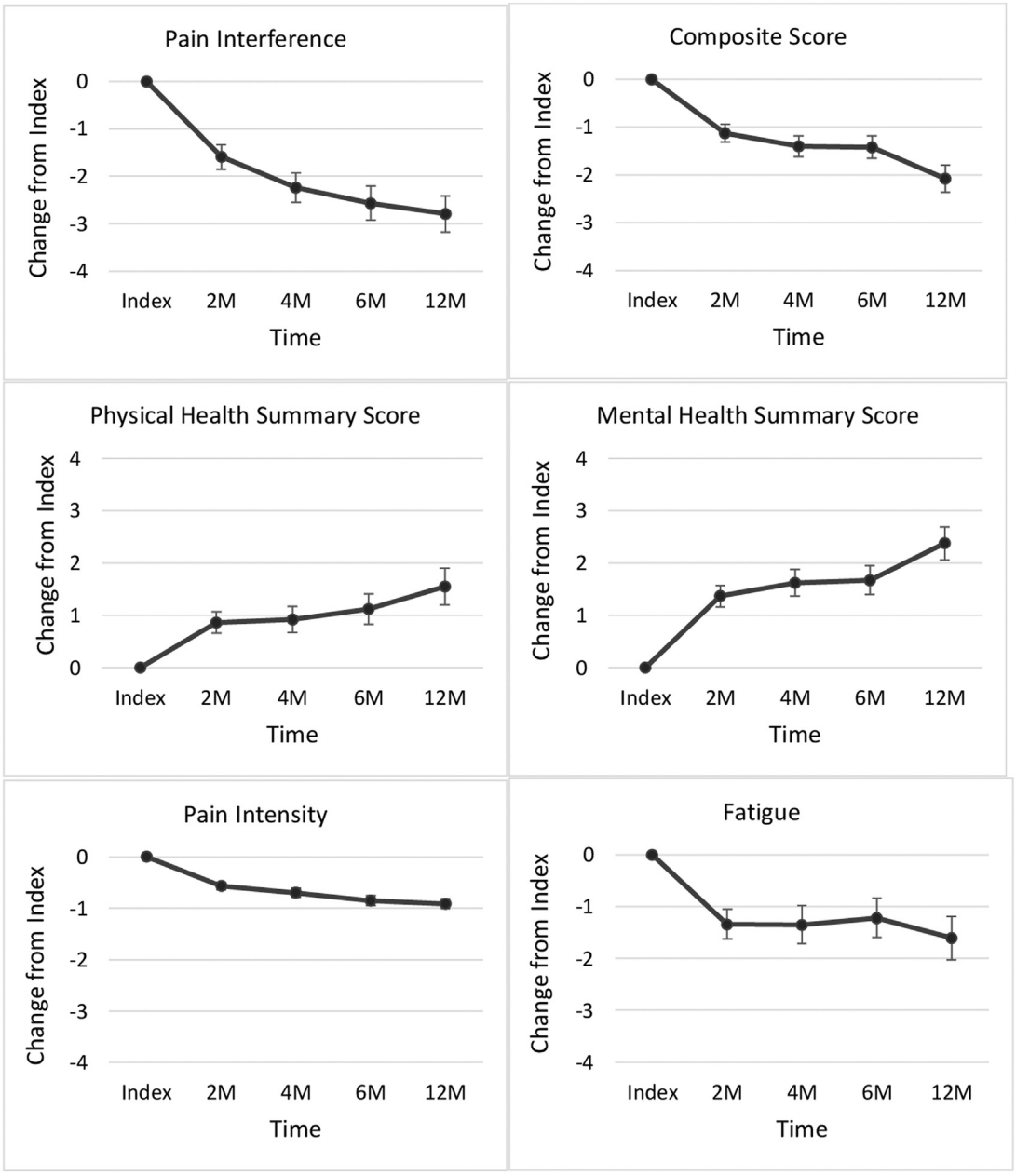

Fig. 2. Unadjusted mean changes from index in select PROMIS-29 scales, PSS, and PAM scores.
Abbreviations: PAM, patient activation measure; PROMIS-29, Patient Reported Outcomes Measurement Information System - 29 Profiles; PSS, Perceived Stress Scale.

3.3.2. Adjusted results

Changes in PROs (PROMIS, PSS, PAM) were adjusted for age and sex with statistical significance assessed via a linear mixed effects model. Like the unadjusted analysis, the adjusted analysis resulted in significant improvements at 12 months ($p < 0.001$) on the primary outcome, PROMIS-29 Pain Interference, the other 6 PROMIS-29 sub-scales, Mental Health and Physical Health Summary scores, Composite score, the PSS-4, and PAM. PROMIS-29 pain interference, pain intensity, fatigue, Mental Health Summary Score, Physical Health Summary Score, and the Composite Score were all significantly improved at all 4-follow-up time-points ($p < 0.001$) (see Table 3). Specific to pain, there was an improvement of 4 % in Pain Interference and improvement 6 % in Pain Intensity from index to 12 months.

Perceived stress (PSS) and patient activation (PAM) scores were significantly improved at 12 months compared to index ($p < 0.0001$), with a 17 % improvement in stress and 4 % improvement in patient activation. Perceived stress scores were also significantly improved at 2 and 4 months compared to index ($p < 0.0001$). Patient activation scores were not significant at any other time point (see Table 3).

3.3.3. Sensitivity analysis

A sensitivity analysis with stabilized inverse probability weights revealed similar findings for unadjusted (stratified by visits) and adjusted analyses for the PROMIS-29 Pain Interference score when accounting for loss-to-follow-up (see Supplemental Table S3).

3.3.4. Minimal clinical important difference

As shown in Table 4, we calculated the minimal clinical important difference (MCID) to determine whether statistically significant changes are clinically meaningful for individual patients. The MCID was calculated for individual patients as $a \geq 3$ point improvement on each of the PROMIS-29 subscales, the Mental Health, and Physical Health Summary

Table 3
Adjusted mean change in PROMIS-29 Mental Health Summary scores, Physical Health Summary scores, Composite score, PROMIS-29 subscales, PSS and PAM scores.

Outcomes	Index Mean (SD)	Adjusted[$] 2M Mean change (95 % CI)	Adjusted[$] 4M Mean change (95 % CI)	Adjusted[$] 6M Mean change (95 % CI)	Adjusted[$] 12M Mean change (95 % CI)
Primary Outcome					
Pain Interference[#]	61.9 (7.8)	−1.56 (−2.07,−1.04)**	−2.18 (−2.74, −1.63)**	−2.54 (−3.13, −1.95)**	−2.70 (−3.31, −1.95)**
Secondary Outcomes					
PROMIS-29 Subscales					
Anxiety[#]	56.4 (9.1)	−0.62 (−1.17, −0.08)	−0.57 (−1.16, 0.02)	−1.13 (−1.75, −0.50)*	−2.20 (−2.84, −1.56)**
Depression[#]	53.4 (9.1)	−0.64 (−1.16, −0.12)	−0.88 (−1.44, −0.31)	−1.23 (−1.84, −0.63)*	−2.16 (−2.78, −1.55)**
Fatigue[#]	59.0 (10.0)	−1.24 (−1.81, −0.67)**	−1.45 (−2.07, −0.82)**	−1.51 (−2.17, −0.85)**	−1.52 (−2.20, −0.85)**
Sleep Disturbance[#]	54.3 (8.1)	−1.08 (−1.59, −0.56)*	−1.00 (−1.57, −0.44)*	−0.99 (−1.59, −0.40)	−1.56 (−2.17, −0.95)**
Social Role[@]	45.2 (8.3)	0.74 (0.25, 1.24)	1.18 (0.64, 1.73)**	1.46 (0.89, 2.04)**	2.02 (1.43, 2.60)**
Physical Function[@]	42.0 (7.9)	0.49 (0.08, 0.89)	0.51 (−0.07, 0.95)	0.69 (0.23, 1.16)	1.13 (0.66, 1.61)**
Pain Intensity	5.6 (1.91)	−0.58 (−0.72, −0.45)**	−0.67 (−0.82, −0.53)**	−0.85 (−1.01, −0.70)**	−0.35 (−1.01, −0.69)**
PROMIS-29 Summary Scores					
Mental Health[@]	41.9 (7.6)	1.32 (0.91, 1.72)**	1.65 (1.21, 2.09)**	1.81 (1.34, 2.27)**	2.23 (1.75, 2.71)**
Physical Health[@]	41.2 (7.9)	0.74 (0.33, 1.14)*	0.90 (0.46, 1.35)**	1.12 (0.65, 1.59)**	1.53 (1.05, 2.02)**
Composite[#]	57.0 (6.5)	−0.58 (−0.72, −0.45)**	−0.67 (−0.82, −0.53)**	−0.85 (−1.01, −0.70)**	−0.85 (−1.01, −0.69)**
Other Scores					
PSS Score[#]	6.3 (3.4)	−0.60 (−0.82, −0.39)**	−0.55 (−0.79, −0.32)**	−0.37 (−0.62, −0.13)	−1.08 (−1.35, −0.84)**
PAM Score[@]	64.1 (15.8)	1.39 (0.39, 2.39)	0.82 (−0.27, 1.92)	1.81 (0.66, 2.98)	2.77 (1.60, 3.96)**

Abbreviations: CI, confidence interval; M, months; PAM, patient activation measure; PROMIS-29, Patient Reported Outcomes Measurement Information System - 29 Profiles; PSS, Perceived Stress Scale; SD, standard deviation.
[$] Adjusted for age and sex.
[#] Mean scores should decrease if patient improves.
[@] Mean scores should increase if patient improves.
* $p < 0.001$;.
** $p < 0.0001$.

Table 4
Proportion of participants (N = 967) meeting Minimal Clinical Important Difference (MCID) on PROMIS-29.

Measure	2 months N = 724	4 months N = 602	6 months N = 519	12 months N = 620
Primary outcome				
Pain interference	226 (36.0 %)	191 (37.8 %)	178 (41.6 %)	178 (43.6 %)
Secondary outcomes				
PROMIS-29 subscales				
Anxiety	209 (32.4 %)	171 (33.3 %)	163 (36.4 %)	173 (40.7 %)
Depression	190 (29.6 %)	165 (32.2 %)	143 (32.4 %)	159 (37.8 %)
Fatigue	241 (37.5 %)	196 (38.7 %)	172 (38.9 %)	160 (38.0 %)
Sleep	227 (35.7 %)	187 (36.7 %)	154 (35.3 %)	164 (39.7 %)
Physical function	151 (23.3 %)	121 (23.5 %)	125 (28.5 %)	124 (29.5 %)
Social role	221 (34.4 %)	175 (34.5 %)	163 (36.9 %)	177 (42.1 %)
PROMIS-29 Summary Scores				
Composite score	175 (30.4 %)	152 (33.3 %)	128 (32.6 %)	145 (39.2 %)
Physical health	156 (26.1 %)	119 (25.4 %)	117 (28.8 %)	130 (34.0 %)
Mental health	219 (36.7 %)	178 (38.0 %)	152 (37.4 %)	165 (43.2 %)

Abbreviations: PROMIS-29, Patient Reported Outcomes Measurement Information System - 29 Profile.

scores as well as the Composite score.[17,18] Between 24 %–44 % of participants met criteria for a clinically important improvement across all outcomes and time points, with the highest percentage being for pain interference at 12 months (44 % met MCID) .[25]

3.3.5. Index visit factors that affect the trend of pain reduction

To understand the index visit factors that affect the trajectory of pain reduction, a longitudinal model of pain reduction, chosen through the backward variable selection method, is shown in Table 5. The predictors at the index visit of the greater rate of pain reduction were high index pain level ($p < 0.00001$), and employment status ($p < 0.0005$), with patients that work part-time or that are unemployed with other responsibilities having the greatest rate of pain reduction. We observed similar results when we repeated the analysis with opioid prescription history forced as a covariate in the model. As shown in Supplemental Table S4, opioid prescription history was not significant.

4. Discussion

To the best of our knowledge, with 3658 enrollees PRIMIER is the largest prospective, longitudinal, observational study of IM examining the effectiveness and outcomes of care in multiple IM clinics.[15] In this cohort of 967 PRIMIER participants with chronic pain we observed changes in PROs after IM services, with the most common services being IM consultations, acupuncture, and manual therapies. Significant improvements were observed at 12-months for all 7 PROMIS-29 subscales across all 4 time periods except physical functioning at 2 and 4-months. Importantly, between 24 % and 44 % of participants met criteria for a clinically important improvement across all outcomes and time points, with the highest percentage being for pain interference at 12 months (44 % met MCID) .[25]

Chronic pain is one of the most common reasons individuals seek IM therapies.[2] In a systematic review of observational and effectiveness studies of individualized IM therapies for acute and chronic pain, Dyer and colleagues[24] found 23 studies with the majority focusing on

Table 5
Multivariate analysis of baseline predictors that affect the trajectory of pain reduction.

Index Variables	Estimate (additional change in Pain Interference per year)	P-Value
PAM score at Index	−0.02966	0.11113
Employment = part-time & unemployed with other responsibilities (vs. full-time)	−1.53674	0.00033
Employment = retired	−0.73068	
Employment = medical leave & unemployed and looking for work	2.65942	
IM use in prior 6 months	−1.18400	0.15738
Pain Interference at index		
Medium [58.5–65.2) (vs. low)	−2.67907	0.00000
High ≥ 65.2	−6.18149	
Male	0.29198	0.69521
Age at index = 40–59 (vs. 18–39)	−0.62268	0.60429
Age at index ≥60	0.07324	
Site (17 sites)	Not shown	0.06197

Abbreviations: IM, integrative medicine; PAM, patient activation measure.

chiropractic, acupuncture, and/or multi-modal individualized interventions/programs. While all 23 studies report beneficial impact on at least one measure of pain (intensity, interference and/or disability), the most common outcome (10 studies) measured was pain intensity on a 0–10 numeric rating scale (NRS). With respect to PROMIS measures, only 2 (9 %) studies used PROMIS measures for pain intensity and interference.[23] Those studies reported an 18 % improvement in pain intensity[26] and between 4 % and 16 % improvement in pain interference, following chiropractic care.[25,26] As mentioned above, we found between a 6 %–15 % improvement in pain intensity and a 3 %–4 % improvement in pain interference across all time points for patients receiving any type of IM service. Nevertheless, the lack of a common set of PRO measures, such as PROMIS Pain Interference, to assess the impact of IM interventions in observational effectiveness research for chronic pain is an ongoing concern for implementation of IM therapies in clinical settings.[23]

Stress is an important mediator of chronic pain and stress management therapies can have direct and indirect impact on the experience of pain.[5] Systematic reviews and meta-analyses have found consistent significant improvements in stress with IM therapies.[27,28] We found improvements of 10 %, 9 %, and 17 % in PSS scores at 2, 4, and 12 months, respectively. Similarly, other observational studies have reported 12 % reduction in stress at 3 months following multimodal IM treatment.[9]

Scores on the patient activation (PAM) was significantly improved for the cohort at each time point except 4 months. Individuals with highest patient activation levels are resilient, proactive with their health, and have self-management skills and patient activation is associated with fewer ER visits hospitalizations, and greater medication adherence in patients with chronic illnesses.[29] Longitudinal increases on the PAM are correlated with decreased pain and a reduction in ER visits.[30] Several previous IM studies have included the PAM and have found similar improvements following multimodal IM programs as the current study.[31-33]

Pain interference ($p < 0.00001$) and employment type ($p < 0.0005$) were baseline predictors of greater pain reduction during the first 12 months. Other studies have also reported higher baseline pain as a predictor variable for improvements in pain following multimodal IM care,[9] as well as duration of pain (e.g., number of years with chronic pain) following multimodal[9] and chiropractic care.[34] Further research with multivariate analyses is recommended to better understand predictor variables for improvements in outcomes.[24]

4.1. Limitations

There are several limitations of the current study. First, the attrition rate was 37 % meaning that numerous participants were not included in the final analyses. There were some differences between the groups. Therefore, this study's results are based on a subset of the full cohort who ere slightly older, more likely to have used IM in the prior 6 months, less likely to be enrolled on their first visit, and who generally has better health as indicated by scores on all the PROs. Nevertheless, according to a recent systematic review of IM practice-based research,[24] the 37 % attrition rate is not atypical of multisite IM effectiveness studies for pain that do not offer participants financial incentives. Additionally, the sensitivity analysis results indicate similar findings for the PROMIS-29 Pain Interference score when accounting for loss-to-follow-up. Second, the sample consisted of mostly highly educated, middle-aged, White women. While this may be the 'typical' demographic of those seeking IM care, including more diverse samples would expand generalizability to other populations. Third, there was no control group, meaning we cannot estimate what proportion of the observed benefits can be attributed to the IM intervention(s). It is possible that improvements were related to the degree of attention participants received at our centers, or a natural improvement over time. Nevertheless, a significant number of participants achieved clinically significant improvements on all PROMIS-29 subscales across 12 months. Fourth, this study is exploratory in nature, and therefore, multiple testing adjustments were not made. In addition, statistical methods for post-selection inference are currently unavailable for mixed effects models. The reported statistical significance should be interpreted appropriately, with further validation needed. Fifth, we did not examine whether a given patient's dose of IM was associated with improved outcomes. With the breadth of the results already presented, a deeper exploration of IM utilization (e.g., dose) is more appropriate for a subsequent publication. Finally, all patients receiving care in a participating site were eligible to join PRIMIER, regardless of whether the index visit was their initial visit or not. Were participation limited to patients who were new to the clinic, or those who had not yet started treatment for their chronic pain, we speculate that we may have observed larger improvements in PROs.

4.2. Future directions

Both PRIMIER and the Veteran's Administration Office of Patient Centered Care and Cultural Transformation (119 veterans enrolled 3 Veterans Affairs Sites)[35] serve as examples of the strengths of collaborative research. While both efforts served a first step, a future IM practice-based study (PRIMIER 2.0) should be embedded within the electronic health record to reflect the IM clinic population more accurately. Additionally, future research should include a larger number of sites and more diverse participants with a common set of patient-reported pain outcomes. Therefore, a given individual seeking treatment at IM clinics could be offered a choice of intervention(s) that prior practice-based research has shown to be effective for their clinical condition – given individuals' demographics and complete clinical presentation. The recommendation could include a "dose" and/or schedule of IM services, which would foster development of optimized IM pain interventions customized to patient needs and characteristics.

4.3. Conclusion

PRIMIER was the largest prospective, longitudinal, observational study of IM, of which the largest cohort was for chronic pain patients. Significant improvements were seen in pain intensity, pain interference, anxiety, depression, fatigue, sleep, physical function, social role satisfaction, and overall physical and mental health at 12 months in this group of patients who were receiving IM treatment. Therefore, based on lessons learned from PRIMIER, we propose that additional practice-based research with larger number of sites and more diverse participants with a common set of patient-reported pain outcomes in IM is needed to help further guide clinical practice.

Author contributions

Conceptualization: JAD, GAK, RMH, ABS, CJC, DRV, AN, AK, RSK, MDM. Methodology: JAD, MDM, AN, AK, RSK. Formal analysis: RSK, AK, BAB. Investigation: JAD, GAK, RMH, ABS, CJC, DRV, AN, AK, JS, TS, KAF, MDM. Data Curation: RSK, AN, AK, JAD, JS, TS. Writing - Original Draft: JAD, NLD, GAK, RMH, ABS, CJC, DRV, AN, AK, RSK, JS, TS, MDM. Writing - Review & Editing: JAD, NLD, GAK, RMH, ABS, CJC, DRV, AN, AK, RSK, JS, TS, KAF, BAB, MDM. Project administration: JAD, MDM, JS. Funding acquisition: JAD, MDM.

Declaration of competing interests

The authors declare that they have no competing interests.

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Ethical statement

All participants provided electronic informed consent before initiation of any study-related procedures. They could provide informed consent via pen and paper if computer access was an issue. The protocol was approved by the Institutional Review Board (IRB) at each participating site. The Duke University Health Systems (previous IRB) and the Einstein Human Research Protection Program (current IRB) approved the study as the BraveNet Data and Statistical Coordinating Center. The study is registered in Clinical Trials.gov (NCT01754038).

Data availability

The authors confirm that the data supporting the findings of this study are available within the article and/ its supplementary materials.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.imr.2025.101141.

Table S1: BraveNet PBRN PRIMIER sites and Chronic Pain Cohort enrollment.

Table S2: Unadjusted mean changes in PROMIS-29, PSS, and PAM scores at each time point.

Table S3: Sensitivity Analysis for PROMIS pain interference score.

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