Evaluating the Utility of Patient-Identified Most Bothersome Symptom for Migraine Research

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Introduction

- Alongside headache pain, clinical manifestations defining migraine include nausea, photophobia, and phonophobia.[1,2]
  - Assessment of the impact of treatment on these cardinal features forms the basis of many migraine clinical trials.[3]
- However, many patients with migraine report additional, less acknowledged symptoms, including allodynia, anorexia, vestibular disturbances, psychiatric manifestations, neck pain, cognitive dysfunction, osmophobia, and fatigue.[4,5]
  - The impact of investigational treatments on these symptoms is often not evaluated in clinical trials,[4] even though they may influence satisfaction with migraine treatment,[6] which in turn contributes to therapeutic persistence/adherence.[7]
  - Analysis of the impact of preventive treatment on the symptom each patient considers most bothersome is not typically studied and could offer critical insights into the overall benefit of preventive therapy.
- The PROMISE-2 study was a phase 3 clinical trial that evaluated intravenously (IV) administered eptinezumab for the preventive treatment of chronic migraine (CM).[8]
  - The study was designed to include a range of patient-reported outcome measures (PROMs).
  - A unique patient-identified most bothersome symptom (PI-MBS) measure was included as a secondary endpoint: instead of having patients select their MBS from a predefined list of potential associated symptoms, each participant was asked to self-identify their most bothersome migraine-associated symptom using an open-ended question.

Objective

- To evaluate the convergent validity of PI-MBS as an outcome measure for the preventive treatment of CM and to assess the potential clinical and research utility of this unique patient-centric tool

Methods

Study Design, Patients, and Treatment Interventions

- PROMISE-2 (NCT02974153)[8] was a randomized, double-blind, placebo-controlled, parallel-group trial that evaluated the preventive efficacy, tolerability, and safety of eptinezumab in adults with a diagnosis of migraine[9] and a history of CM for ≥12 months.
- Eligible patients were randomized to receive intravenous eptinezumab 100 mg, 300 mg, or placebo every 12 weeks for up to 2 doses (24 weeks of treatment).

PI-MBS

- Patients were asked to verbally describe the MBS that they associated with their CM at the screening visit. These verbatim descriptions were categorized by investigators into a predefined list of symptoms (including an "other" category with free-text description), which was used as the reference for reporting improvements at subsequent visits.
- At Week 12, patients rated the overall improvement from baseline in their PI-MBS on an ordinal scale (1=very much worse, 2=much worse, 3=minimally worse, 4=no change, 5=minimally improved, 6=much improved, and 7=very much improved).
- To evaluate whether relationships between PI-MBS improvement and other PROMs remained similar across differing symptom types, we conducted a sensitivity analysis in which symptoms were reduced into three broad classes.
  - Pain-related: eye pain, headache, pain, pain-anatomical, pain with activity, and throbbing/pulsation
  - Cardinal: nausea/vomiting, sensitivity to light, and sensitivity to sound
  - Other: allodynia, aura, cognitive disruption, dizziness, fatigue, inactivity, mood changes, neck pain, pressure/tightness, sensitivity to smell, sensory disturbance, sleep disturbance, speech difficulty, vision impacts, multiple, and other

Other PROMs Collected in PROMISE-2

- Change in monthly migraine days (MMDs) from baseline to Weeks 9–12
- Patient Global Impression of Change (PGIC)[10] at Week 12
- Change in the 36-Item Short-Form Health Survey (SF-36)[11] Physical Component Summary (PCS) and the Mental Component Summary (MCS) scores from baseline to Week 12
- Change in the EuroQoL 5-Dimension 5-Level (EQ-5D-5L)[12] visual analog scale (VAS) score from baseline to Week 12
- Change in the 6-Item Headache Impact Test (HIT-6)[13] total scores from baseline to Week 12

Statistical Analyses

- Analyses were conducted to assess the convergent validity and clinical utility of the PI-MBS.
- First, we explored whether different classes of PI-MBS could be combined for subsequent analyses, with $P>0.05$ providing support for pooling symptoms.
- Then, we explored the relationship between PI-MBS and related PROMs.
  - Pearson correlations (parametric) and Spearman correlations (non-parametric) were estimated to evaluate the convergent validity of PI-MBS improvement with other PROMs.
  - Linear and ordinal (proportional odds) regression models were used to evaluate the unique effects of PI-MBS on PROMs controlling for changes in MMDs.
- To estimate the magnitude of eptinezumab treatment effects, linear regression models were fit using PI-MBS improvement and MMD change as dependent variables, as well as the other PROMs.

Results

Patients and PI-MBS at Baseline

- A total of 1072 adults with CM participated in PROMISE-2 (mean age 40.5 years; 88.2% female; 91.0% white). The mean age at migraine diagnosis was 22.5 years, the mean duration of CM was 11.8 years, and the mean number of migraine days during screening was 16.1.[8]
- Patients reported a total of 23 unique PI-MBS (**Table 1**). More than 80% of patients identified a symptom that fell within either the pain-related (43.1%) or cardinal (41.0%) PI-MBS classes.

Table 1. Categories of PI-MBS at PROMISE-2 Screening

Patients, n (%)	Total (N=1072)
Pain-Related Symptoms	462 (43.1)
Pain exacerbation with activity[a]	147 (13.7)
Pain[a,b]	133 (12.4)
Headache[a]	120 (11.2)
Throbbing/pulsation[a]	50 (4.7)
Eye pain[b]	6 (0.6)
Anatomical pain[b]	6 (0.6)
Cardinal/Traditional Symptoms	440 (41.0)
Sensitivity to light[a]	200 (18.7)
Nausea/vomiting[a]	162 (15.1)
Sensitivity to sound[a]	78 (7.3)
Other Symptoms	170 (15.9)
Cognitive disruption	44 (4.1)
Fatigue	26 (2.4)
Mood changes	16 (1.5)
Sensitivity to smell	10 (0.9)
Visual impact[c]	8 (0.7)
Aura	7 (0.7)
Pressure/tightness	7 (0.7)
Dizziness	5 (0.5)
Neck pain	5 (0.5)
Allodynia	3 (0.3)
Inactivity	2 (0.2)
Sensory disturbance[c]	1 (0.1)
Sleep disturbance	1 (0.1)
Speech difficult[c]	1 (0.1)
Multiple[d]	27 (2.5)
Other	7 (0.7)

[a]Included in the ICHD-3 diagnostic criteria.
[b]Extra-cephalic pain (patients were not limited in their description of PI-MBS).
[c]Could be related to ICHD-3 cardinal symptoms such as aura and photophobia or other visual impacts not considered migraine-defining, such as blurry vision.
[d]Patient reported >1 type of PI-MBS.
ICHD-3, International Classification of Headache Disorders, 3rd edition; PI-MBS, patient-identified most bothersome symptom.

Classes of PI-MBS

- There was preliminary support for pooling PI-MBS over three classes: pain-related, cardinal, and other.
- Demographics and baseline clinical characteristics stratified by PI-MBS class are shown in **Table 2**.
  - PI-MBS classes did not differ with regard to sex ($P=0.3282$), age of migraine diagnosis ($P=0.5122$), or screening migraine days ($P=0.5298$).
  - While the PI-MBS classes did statistically differ by age ($P=0.0164$) and duration of migraine diagnosis ($P=0.0110$), the numerical differences were small and did not appear clinically meaningful.

Table 2. Demographics and Baseline Clinical Characteristics in PROMISE-2 Grouped by PI-MBS Class

	Pain-Related (N=462)	Cardinal (N=440)	Other (N=170)
Age (years), mean (SD)	41.7 (11.0)	39.7 (11.1)	39.8 (11.5)
Sex, n (%)			
Male	62 (13.4)	47 (10.7)	17 (10.0)
Female	400 (86.6)	393 (89.3)	153 (90.0)
Race, n (%)			
White	438 (94.8)	388 (88.2)	149 (87.6)
Black or African American	21 (4.5)	44 (10.0)	17 (10.0)
Other[a]	3 (0.7)	8 (1.8)	4 (2.4)
Age at migraine diagnosis (years), mean (SD)	22.4 (10.6)	22.8 (9.4)	21.8 (9.8)
Duration of migraine diagnosis (years), mean (SD)	19.2 (11.7)	16.9 (11.7)	18.0 (12.0)
Screening period migraine days, n (%)			
<17 days	252 (54.6)	237 (53.9)	100 (58.8)
≥17 days	210 (45.5)	203 (46.1)	70 (41.2)
Treatment group, n (%)			
Eptinezumab 100 mg	158 (34.2)	144 (32.7)	54 (31.8)
Eptinezumab 300 mg	154 (33.3)	138 (31.4)	58 (34.1)
Placebo	150 (32.5)	158 (35.9)	58 (34.1)

[a]Other includes Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple races, and other.
PI-MBS, patient-identified most bothersome symptom; SD, standard deviation

- Relationships among the PROMs did not significantly differ across the three PI-MBS classes ($P=0.0523$).
- At Week 12, PI-MBS classes did not significantly differ in reported improvement ($P=0.2099$; **Table 3**).

Table 3. PI-MBS Improvement at Week 12 Grouped by PI-MBS Class

Patients, n (%)	Pain-Related (N=462)	Cardinal (N=440)	Other (N=170)
Very much worse	0	0	1 (0.6)
Much worse	5 (1.1)	1 (0.2)	0
Minimally worse	12 (2.7)	7 (1.7)	7 (4.4)
No change	99 (22.3)	83 (19.7)	32 (20.0)
Minimally improved	118 (26.6)	106 (25.2)	46 (28.8)
Much improved	135 (30.4)	152 (36.1)	47 (29.4)
Very much improved	75 (16.9)	72 (17.1)	27 (16.9)

Note: PI-MBS classes did not significantly differ in reported improvement based on ordinal proportional odds ($\chi^2(2) = 3.12$, $Pr(>\chi^2)=0.2099$) or ANOVA model ($F(2, 1022) = 1.91$, $Pr(>F)=0.1481$) results.
PI-MBS, patient-identified most bothersome symptom.

Convergent Validity and Regression Analyses

- Correlations among PI-MBS improvement and changes in theoretically related PROMs at Week 12 are shown in **Table 4**.
  - PI-MBS improvement at Week 12 was significantly correlated with changes or improvement on all other PROMs evaluated ($P<0.0001$).
  - The magnitudes of the correlations were closely aligned with clinical theory, with strong correlations between PI-MBS improvement and changes in headache-/migraine-specific outcomes (HIT-6 total scores and MMDs; $r\sim-0.5$) and weaker correlations between PI-MBS improvement and changes in more general (less CM-specific) PROMs (SF-36 PCS, SF-36 MCS, and EQ-5D-5L VAS; $r=0.21$–0.35).
  - The correlation between PI-MBS improvement and PGIC was very strong ($r\sim0.85$), as expected given the similarity between the content and responses.

Table 4. Relationships Between Improvement in PI-MBS and Changes in PROMs at Week 12

	PI-MBS	ΔMMDs	ΔHIT-6	PGIC	ΔEQ-5D-5L	ΔSF-36 PCS	ΔSF-36 MCS
PI-MBS	1.00	-0.49	-0.53	0.85	0.25	0.35	0.22
ΔMMDs	-0.49	1.00	0.49	-0.49	-0.22	-0.29	-0.26
ΔHIT-6	-0.50	0.48	1.00	-0.57	-0.36	-0.43	-0.39
PGIC	0.84	-0.49	-0.54	1.00	0.28	0.34	0.28
ΔEQ-5D-5L	0.25	-0.21	-0.37	0.28	1.00	0.38	0.31
ΔSF-36 PCS	0.34	-0.29	-0.45	0.34	0.39	1.00	0.11
ΔSF-36 MCS	0.21	-0.28	-0.42	0.27	0.35	0.13	1.00

Pearson correlations are on bottom diagonal (below 1's) and Spearman correlations are on top diagonal (above 1's).
Δ, mean change from baseline to Week 12; EQ-5D-5L, EuroQol 5-Dimension 5-Level (visual analog scale); HIT-6, 6-Item Headache Impact Test; MCS, Mental Component Summary score; MMDs, monthly migraine days; PCS, Physical Component Summary score; PGIC, Patient Global Impression of Change; PI-MBS, patient-identified most bothersome symptom; PROMS, patient-reported outcomes measures; SF-36, 36-item Short-Form Health Survey.

- PI-MBS improvement significantly predicted better outcomes above and beyond change in the MMDs ($P<0.01$ for all).
  - For four of the five PROMs (all but SF-36 MCS), PI-MBS had larger standardized effects compared with change in MMDs (**Table 5**).

Table 5. Standardized Regression Coefficients for MMD and PI-MBS Effects on Related PROMs

	ΔHIT-6		PGICa		ΔEQ-5D-5L		ΔSF-36 PCS		ΔSF-36 MCS	
	Std est.	P value	Std est.	P value	Std est.	P value	Std est.	P value	Std est.	P value
ΔMMDs	0.31	<0.0001	-0.21	<0.0001	-0.12	0.0006	-0.16	<0.0001	-0.23	<0.0001
PI-MBS	-0.35	<0.0001	1.82	<0.0001	0.19	< 0.0001	0.27	<0.0001	0.10	0.003

[a]Based on ordinal proportional odds model.
Δ, mean change from baseline to week 12; EQ-5D-5L,EuroQol 5-Dimension 5-Level (visual analog scale); HIT-6,6-Item Headache Impact Test; MCS, Mental Component Summary score; MMDs, monthly migraine days; PCS, Physical Component Summary score; PGIC, Patient Global Impression of Change; PI-MBS, patient-identified most bothersome symptom; PROMS, patient-reported outcomes measures; SF-36, 36-item Short-Form Health Survey; Std est., standardized estimate.

Treatment Effect Sizes

- The treatment effects on PI-MBS improvement were generally larger than on other PROMs, as well as changes in MMDs.
  - For patients receiving eptinezumab 300 mg, the overall effect size versus placebo was 0.54 ($P<0.0001$).
  - For those receiving 100 mg, the effect size versus placebo was slightly smaller (0.31; $P<0.0001$).

KEY POINTS

- **For the novel patient-identified most bothersome symptom (PI-MBS) measure captured in PROMISE-2, instead of patients selecting their MBS from a predefined list of potential associated symptoms, each patient was asked to self-identify their most bothersome migraine-associated symptom using an open-ended question.**
- **The results of these analyses suggested that the 23 total unique symptoms identified by patients could be pooled into a single PI-MBS measure.**
- **PI-MBS improvement at week 12 correlated in expected ways with changes in MMDs, HIT-6, PGIC, EQ-5D-5L, and SF-36 at week 12 (all $P<0.001$).**
- **The finding that PI-MBS improvement at week 12 consistently predicted improvement on PROMs, controlling for MMD changes, suggests that the PI-MBS may provide utility for preventive migraine research and clinical practice.**

CONCLUSIONS

- **These exploratory analyses of data from the PROMISE-2 study suggest that PI-MBS may provide additional benefits for migraine research compared with other commonly evaluated PROMs.**
- **PI-MBS improvement correlated with PROMs and showed unique effects above and beyond changes in MMDs.**
- **PI-MBS may provide a unique measure for assessing patient-centered aspects of burden of disease and benefits of treatment, providing insights beyond the standard measure of MMDs.**
  - **Thus, clinicians, trialists, and policymakers should consider longitudinal monitoring of PI-MBS when evaluating the efficacy of preventive migraine treatments.**

References

1. Headache Classification Committee of the IHS. *Cephalalgia*. 2018;38(1):1-211. **2.** Munjal S, et al. *Headache*. 2020;60(2):416-429. **3.** Houts CR, et al. *Headache*. 2021;61(2):263-275. **4.** Chen PK, Wang S. P1000Res: 2018;7:188. **5.** Lipton RB, et al. *Headache*. 2018;58(9):1408-1426. **6.** Davies GM, et al. *Cephalalgia*. 2000;20(6):554-560. **7.** Bartosca CD, et al. *Patient Prefer Adherence*. 2012;6:39-48. **8.** Lipton RB, et al. *Neurology*. 2020;94:e1365-e1377. **9.** Headache Classification Committee of the IHS. *Cephalalgia*. 2013;33(9):629-808. **10.** Guy W. DHEW Publication No. ADM 76–338. US Government Printing Office, Washington, DC, USA; 1976. **11.** Ware JE Jr. *Spine (Phila Pa 1976)*. 2000;25(24):3130-3139. **12.** Herdman M, et al. *Qual Life Res*. 2011;20:1727-1736. **13.** Kosinski M, et al. *Qual Life Res*. 2003;12(8):963-974.

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