Generalized Healthy-Time Equivalents for Migraine-Treatment Outcomes From Choice-Experiment Trade-off Preferences

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INTRODUCTION

- Migraine is a chronic neurologic disorder characterized by episodes of headache lasting 4 to 72 hours and can include symptoms such as nausea, vomiting, and sensitivity to light and to sound.
- The impact of migraine on patients is commonly divided between the level of impairment experienced during a migraine attack (ictal burden) and quality-of-life effects that go beyond migraine attacks (interictal burden).
- Although ictal burden is an obvious source of impairment for migraineurs, recent evidence suggests that it only partly predicts the level of interictal burden.[1-3]
- Evaluations of productivity losses and health-related quality-of-life questionnaires have proved useful as a way to understand ictal and interictal burden, but do not fully assess the relative impact of ictal and interictal burden from a patient perspective.

OBJECTIVE

- This study aims to quantify patients' preferences for ictal and interictal burden and examine the tradeoffs migraineurs are willing to accept between severity and clinically relevant durations of migraine symptoms.

STUDY DESIGN AND METHODS

Sample

- 539 adults with self-reported physician diagnosis of migraine completed an online survey.
- 29 (5.4%) subjects reported symptoms consistent with cluster headaches rather than migraines. We excluded these 29 observations, leaving a final sample size of 510.

Methods

- We elicited trade-off preferences for time with headache symptoms of specified severity, postheadache limitations, and symptom-free time using best-practice discrete-choice experiment or choice-format conjoint-analysis methods.[4-8]
- Generalized healthy-time equivalents (HTEs) indicate time with no symptoms that yields the same subjective level of well-being as a specified spell of ill health, described by a profile of symptoms with a given duration.
- We calculated HTEs to compare the relative severity of different migraine-event profiles.

Why Not QALYs?

- Quality-adjusted life-years (QALYs) require eliciting tradeoffs involving mortality risks (standard gamble) or longevity (time tradeoff), which are clinically irrelevant for acute, self-limiting conditions such as migraine headaches. QALYs also require strong linearity and additivity assumptions that are inconsistent with stated and revealed preferences.
- HTEs avoid many of the restrictive assumptions of QALYs. Unlike QALYs, HTEs are based on nonlinear trade-off preferences for clinically relevant outcomes and durations.[9]

Survey Instrument

- A Web-enabled survey instrument was used to collect information.
- Table 1 contains the migraine-related attributes included in the survey.
- Subjects evaluated eight pairs of migraine profiles and indicated the alternative they would choose if these were the only options available (Figure 1).
- The combination of severity levels and durations in each profile were determined using an experimental design with known statistical properties.[10-11] The experimental design:
  - Reduced the number of paired comparisons to the smallest number necessary for efficient estimation of preference weights.[10-11]
  - Blocked the paired comparisons into eight sets of choice questions. Subjects were randomly assigned to one of the resulting eight versions of the survey.

Analysis

- Preference-weight estimation was completed using a multivariate, random-parameters or mixed-logit choice model.[12,13]

Table 1. Migraine Attributes and Levels

Attributes	Levels
Severity of headache symptoms (ictal burden)	Throbbing with no sensitivity to light and sound or severe nausea Throbbing head pain and sensitivity to light and sound, no severe nausea Throbbing head pain and severe nausea, no sensitivity to light and sound Throbbing head pain, sensitivities to light and sound, and severe nausea
Duration of headache symptoms (ictal burden)	30 minutes 1 hour 3 hours 8 hours
Severity of postheadache limitations (interictal burden)	No limitations (only shown with "0 hours" postheadache duration) Difficulty doing work and social activities Cannot work or participate in social activities
Duration of postheadache limitations (interictal burden)	None (0 hours) 4 hours 8 hours 16 hours
Symptom-free time	Difference between 24 hours and the sum of the durations of the headache and postheadache phases
Chance headache returns within 24 hours (interictal burden)	No chance 10% chance 33% chance 50% chance

Figure 1. Example Choice Question

RESULTS

Demographic Characteristics (N = 539)

- Mean age: 43.6 (standard deviation = 14.6)
- White: 377 (69.9%)
- Female: 418 (77.6%)
- College degree or higher: 125 (23.2%)
- Working: 278 (51.6%)

Experience With Migraines (N = 539)

- During the headache phase (ictal), most subjects experienced the following symptoms:
  - Sensitivity to light (90%)
  - Throbbing or pounding head pain (86%)
  - Difficulty thinking or concentrating (82%)
  - Pain worsening with activity (76%)
  - Pain on one side of the head (69%)
  - Nausea (69%)
  - Irritability (60%)
  - Neck pain or discomfort (53%)
  - Feeling tired and sluggish (52%)
- After the headache phase (interictal), most subjects felt tired and sluggish (68%).

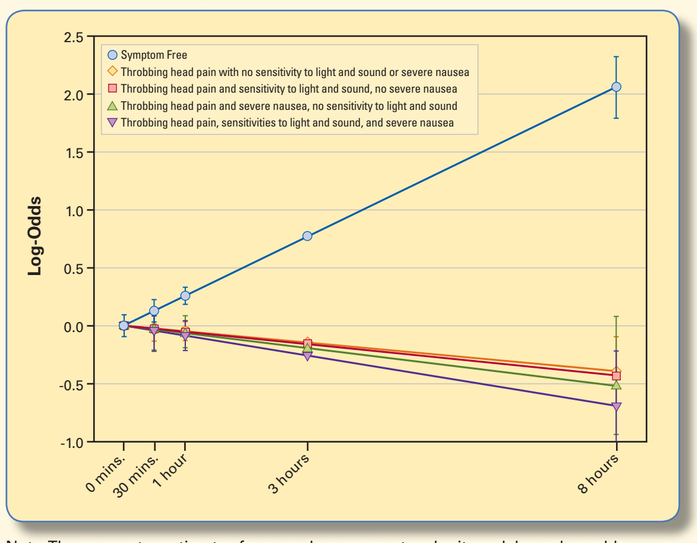
Preference Weights

The parameter estimates from random-parameters logit models can be interpreted as preference weights indicating the relative strength of preference for each attribute level.

Ictal Burden

- Figure 2 presents migraineurs' preference weights for severity and duration of ictal burden.
- Specification tests indicated that preferences for headache-phase (ictal) outcomes are approximately linear in duration.
  - The relative importance of a 1-hour reduction in symptom duration is the same regardless of whether the overall duration from which the reduction occurs is short (e.g., 1.5 hours) or long (e.g., 8 hours).
  - The least preferred outcome in the headache phase is experiencing throbbing head pain, sensitivity to light and sound, and nausea.
  - Results indicate that respondents prefer sensitivity to light and sound to severe nausea.

Figure 2. Preference Weights for Ictal Burden Over Time (N = 510)



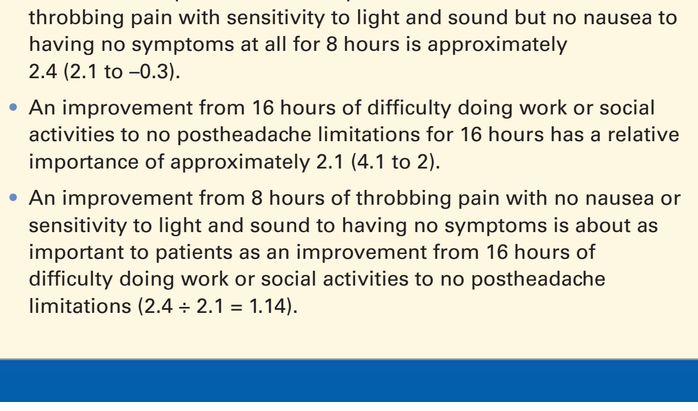
Note: The parameter estimates from random-parameters logit models are log-odds estimates representing the migraine respondents' preferences for attribute level.

Note: The vertical bars around each mean preference weight denote the 95% confidence interval (CI) for the point estimate. Estimates are most accurate for the average number of hours in the headache phase. Hence, CIs of approximately 2.5 hours are the smallest. In several cases, the CI is smaller than the marker used for the point estimate.

Interictal Burden

- Figure 3 presents migraineurs' preference weights for severity and duration of interictal burden.
- Functional-form tests indicated that preferences for the two activity-restriction levels are quadratic in duration, which means that the effect of an additional hour of activity restriction depends on the duration of restrictions.
- Respondents logically prefer having difficulty with work and other social activities to not being able to work or participate in social events.

Figure 3. Preference Weights for Interictal Burden Over Time (N = 510)



Note: The parameter estimates from random-parameters logit models are log-odds estimates representing the migraine respondents' preferences for attribute level.

Note: The vertical bars around each mean preference weight denote the 95% CI for the point estimate. Estimates are most accurate for the average number of hours in the postheadache phase. Hence, CIs of approximately 7 hours are the smallest. In several cases, the CI is smaller than the marker used for the point estimate.

Comparing Ictal and Interictal Burden

For a given duration, the vertical distances between preference weights indicate the relative importance of moving from one attribute level to another attribute level.

- The relative importance of an improvement from 8 hours of throbbing pain with sensitivity to light and sound but no nausea to having no symptoms at all for 8 hours is approximately 2.4 (2.1 to –0.3).
- An improvement from 16 hours of difficulty doing work or social activities to no postheadache limitations for 16 hours has a relative importance of approximately 2.1 (4.1 to 2).
- An improvement from 8 hours of throbbing pain with no nausea or sensitivity to light and sound to having no symptoms is about as important to patients as an improvement from 16 hours of difficulty doing work or social activities to no postheadache limitations (2.4 ÷ 2.1 = 1.14).

Evaluating Migraine Profiles

- Each symptom/duration profile has a preference-weight score that corresponds to an equivalent number of symptom-free hours.
- Table 2 summarizes the number of hours without symptoms or chance of occurrence that yields the same level of well-being as a longer period of time with symptoms and some positive chance of recurrence.
- HTEs can be larger than 24 hours because of the value of low probability of recurrence.
- Figure 4 summarizes the details of each example profile.

Table 2. Comparing Migraine Profiles Using HTE

Symptoms Profile	HTE, Hours	Lower Bound (95% CI)	Upper Bound (95% CI)
Migraine 1	34.80	31.96	37.64
Migraine 2	33.22	30.83	35.60
Migraine 3	23.78	22.01	25.55
Migraine 4	17.82	15.14	20.51
Migraine 5	2.60	1.46	3.74

Figure 4. Migraine Example Profiles

Migraine 1: This is a migraine with mild ictal burden and no interictal burden. Features: headache for 30 minutes, 23.5 hours in the symptom-free phase, and no chance that the same migraine will come back within 24 hours.

Migraine 2: This is the "average" migraine reported by respondents. Features: headache and sensitivity to light and sound for 30 minutes, some activity limitations for 8 hours, 15.5 hours in the symptom-free phase, and a 10% chance that the same migraine will come back within 24 hours.

Migraine 3: This is a migraine with moderate ictal burden and mild interictal burden. Features: headache and sensitivity to light and sound for 1 hour, some activity limitations for 8 hours, 15 hours in the symptom-free phase, and a 33% chance that the same migraine will come back within 24 hours.

Migraine 4: This is a migraine with severe ictal burden and mild interictal burden. Features: headache and nausea for 8 hours, some activity limitations for 8 hours, 8 hours in the symptom-free phase, and a 33% chance that the same migraine will come back within 24 hours.

Migraine 5: This is a migraine with mild ictal burden and severe interictal burden. Features: headache for only 30 minutes, severe activity limitations for 16 hours, 7.5 hours in the symptom-free phase, and no chance that the same migraine will come back within 24 hours.

CONCLUSIONS

- On average, migraineurs considered symptoms such as sensitivity to light and sound, and nausea more harmful than pain alone, but the impact of these additional symptoms was not statistically different from just experiencing pain.
- Migraineurs in our study discriminated clearly among levels of limitations on daily activities.
- Controlling for time with symptoms, ictal burden is considered more harmful by migraineurs.
- Since interictal burden can take longer to resolve, total change in well-being associated with interictal burden can be greater than changes brought upon by symptoms during a migraine attack.
- Results highlight the importance of measuring incidence of interictal burden in the migraineurs. They also suggest that production losses associated with interictal burden may understate the societal impact of migraines.

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