

**Prospective Comparison of Methods for Assessment of Headache Directionality**

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## **Abstract**

Response to prophylactic treatment of migraine with Onabotulinumtoxin A (BTX-A) has been noted to be significantly correlated to the perceived direction of headache pain, namely imploding vs. exploding subtype. This study analyzed 3 methods of assessing migraine directionality (pictorial representation, written description, and physician assessment) in comparison to a 30-day headache. Each of these assessment types was shown to have poor agreement with the headache log at the initial visit. However, all 3 assessments displayed excellent agreement at the return visit, as well as significantly improved confidence in patient ability to determine headache directionality.

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## Introduction/Significance

The Global Burden of Disease Survey 2010 [1] ranks migraine as the third most prevalent disorder, with a lifetime prevalence of 24% in women and 9% in men. Migraine is also ranked as the 7<sup>th</sup> highest specific cause of disability worldwide. Successful management of migraine requires utilization of both prophylactic and abortive therapies. However, individual responses to prophylactic medications are highly variable, and FDA approved migraine prevention treatments were found to be effective in only 200 to 400 patients per 1,000 treated. [2] Currently, there are no known clinical factors that are predictive of patient response, and clinicians must design individual treatments based on trial and error.

Studies of one prophylactic migraine therapy, OnabotulinumtoxinA (BTX-A), have noted that the described direction of headache pain was strongly predictive of patient response to treatment. Specifically, responders were significantly more likely to experience ‘imploding’ headaches, in which their head feels as if it has been “crushed, clamped, or stubbed by external forces”. Non-responders were more likely to experience ‘exploding’ headaches, described as “a painful buildup of pressure inside the head” [3]. Similar studies evaluating the perceived direction of migraine pain in association with response to treatment with onabotulinumtoxin have shown comparable results. [4] The differences in these two groups suggest an underlying difference in pathophysiology that is not well understood. Given the positive response seen in imploding headache, it has been theorized that this subtype involves an interaction with extracranial sensory fibers that is not present in exploding headaches [3]

In these previous studies, imploding and exploding headache subtypes were differentiated using a clinician assessment or patient survey. Given the lack of standardization that currently exists for making this differentiation in subtype, a recent study conducted at a women’s health clinic explored alternate methods of clinician assessment and patient self-assignment. [5] It was found that within individual patients, the assigned headache subtype varied significantly depending on the method of determination, with weak statistical agreement. One plausible explanation is that this variation may be due to patient unfamiliarity with describing headaches in this manner, and therefore the purpose of this study is to

investigate different methods of determining headache directionality subtype and compare these with a 30-day headache log. Because patients would log headaches as they are encountered, we believe that it is at this time that they will be able to most accurately describe the directionality, and thus this log would be used as the gold standard against which to compare other methods of clinical assessment. We hypothesize that at least one method of clinical determination of directionality (either pictorial, standardized subject survey, or standardized investigator conducted survey), will correlate closely with the majority of the subject's self-reported headaches found in the headache log.

## Research Materials and Methods

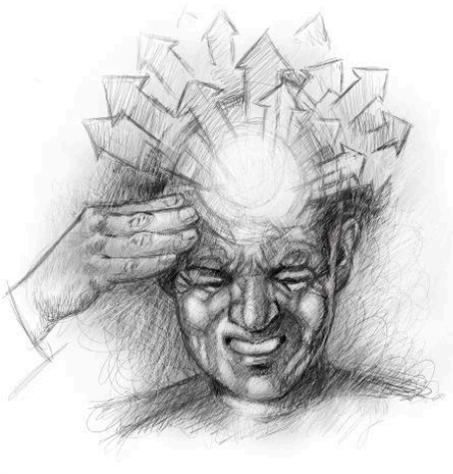
We conducted an institutional review board approved prospective study of 34 patients seen at an outpatient headache neurology clinic from January 2015 to December 2016. Patients included in the study were at least 18 years of age with a primary diagnosis of migraine with or without aura, as determined by the diagnostic criteria included within the International Classification of Headache Disorders III Beta (ICHD III beta). [6] Patients were identified during their office visits in the Mayo Clinic Headache Clinic. Patients were excluded from participation in the study due to patient refusal, inability to read English, visual or communication impairment that resulted in an inability to complete the survey, or a primary diagnosis other than migraine.

After obtaining informed consent, patients completed a self-administered survey and Migraine Disability Assessment (MIDAS) questionnaire. This was followed by a scripted physician interview. Headache directionality was determined via three methods:

1) Pictorial representation:

“Please choose the **one** picture that most accurately represents the **majority** your headaches? Please circle:”

a)



b)



*Figure 1: Illustration utilized in patient surveys to determine headache sub-type*

2) Written question:

“ Would you describe the majority of your headaches as:

- a) A sensation of pain or pressure that builds from within and feels as if your head is expanding; pushing out from the inside
- b) A squeezing, crushing, tightening sensation that feels as if your head is collapsing inward; pushing in from the outside”

3) Physician question with hand gestures:

“Would you describe the **majority** of your headache pain as:

a sensation of pain or pressure that builds from within and feels as if your head is expanding, bursting or splitting open; pushing out from the inside. (hand gesture at temples in opening motion)

or

a sensation of pain or pressure that is squeezing, crushing, or tightening that feels as if your head is collapsing inward; pushing in from the outside. (hand gesture at temples in pressing in motion)”

The physician was blinded to the patient’s answers for method #1 and #2.

The survey also included questions to assess patient confidence in the given responses using a scale of 0 (not confident at all) to 10 (completely confident).

Following completion of these initial assessments, patients were provided with a 30-day headache diary. Patients were instructed to log each day, including days in which no headache occurred. Information gathered included headache direction (simply written as “pushing IN” for imploding, or “pushing OUT” for exploding) and severity. Approximately 2 weeks after the initial office visit, patients received a phone call reminder to complete the diary, and a follow-up appointment was scheduled at this time.

At the completion of 30 days, patients had 15 days to return to clinic for a final assessment. At this visit, patients returned the headache log and completed a follow-up survey and MIDAS questionnaire. This survey was virtually identical to the initial self-administered survey, with the pictorial and written descriptions of headache directionality subtype. This survey also assessed for any change in preventative migraine medications since the initial office visit. The clinician then completed a follow-up scripted assessment, blinded to the self-administered survey results. This survey was also virtually identical to the initial survey, with standardized hand gestures.

### **Statistical Methods**

Dichotomous or categorical variables were summarized as counts and percentages. Continuous variables were summarized as means and standard deviations. Differences between distributions of continuous variables were analyzed by two-tailed and paired t-tests with  $p < .05$  considered significant. Inter-rater agreement was determined via Cohen's kappa coefficient. Kappa  $> 0.8$  was classified as excellent agreement, 0.7-0.79 as good agreement, 0.5-0.69 as moderate agreement, and  $< 0.5$  as poor agreement.

## Results

Thirty-four subjects completed the initial study procedures. Subject demographics and migraine characteristics are shown in Table 1. The average age of subjects was 44 years and 88% were female. The majority of subjects had chronic migraine without medication overuse. The mean number of years with migraine was 19. The subjects were highly educated, with all subjects having at least some college and 41% having a Master's Degree or a Professional/Doctoral Degree.

**Table 1: Subject Demographics and Migraine Characteristics**

<b>Age (mean +/- SD)</b>	44 +/- 14 years
<b>Sex</b>	Male = 4 Female = 30
<b>Headache Diagnosis</b>	Chronic Migraine = 27 Episodic Migraine = 7 Medication Overuse = 4
<b>Headache Frequency per 90 days (mean +/-SD)</b>	37 +/- 30
<b>Years with Migraine (mean +/- SD)</b>	19 +/- 14
<b>Highest Education</b>	Some College, No Degree = 10 Associate Degree = 10 Master's Degree = 9 Professional or Doctoral Degree = 5

At the initial visit, using the pictorial description of headache directionality, 10/34 (29.4%) described the majority of their headaches as exploding and 24/34 (70.6%) described them as imploding. Using the written assessment, 17/34 (50%) described the majority of their headaches as exploding and 17/34 (50%) described them as imploding. Based on the physician question regarding headache directionality, 14/34 (41.2%) patients were considered to have exploding headaches and 20/34 (58.8%) were considered to have imploding headaches. 24/34 (70.6%) patients had the majority of their headaches rated the same way (all imploding or all exploding) using all 3 methods of assignment. 13/33 (39.4%) patients reported that they only had one headache directionality whereas the rest reported that they have a combination of imploding and exploding headaches. Of those who reported that all of their headaches were of one directionality, 10/13 (76.9%) had the majority of their headache rated the same way using all 3 methods of assignment.

Twenty-eight of the 34 subjects returned for the follow-up study visit and provided headache diaries. Based upon headache diaries, 11/28 (39.3%) reported the majority of their headaches to be exploding, 16/28 (57.1%) reported the majority as imploding, and one patient had equal numbers of imploding and exploding headaches. 17/28 (60.7%) patients reported every one of their headaches to have the same directionality. The agreement between ascertaining headache directionality at baseline with diary reporting was 63% for the pictorial description (Cohen's kappa = .24 = poor agreement), 70.4% for the written description (Cohen's kappa = .38 = poor agreement), and 74.1% for the physician question (Cohen's kappa = .46 = poor agreement).

At the return visit, 27 of 28 subjects completed the follow-up questionnaires. Based upon the pictorial method of assignment 9/27 (33.3%) described the majority of their headaches as exploding and 18/27 (66.7%) as imploding. Pre-diary vs. post-diary assignment using this method changed for 9/27 (33.3%) patients. Based upon the written description, 10/27 (37%) described the majority of headaches as exploding and 17/27 (63%) as imploding. Pre-diary vs. post-diary assignment using this method changed for 9/27 (33.3%) patients.

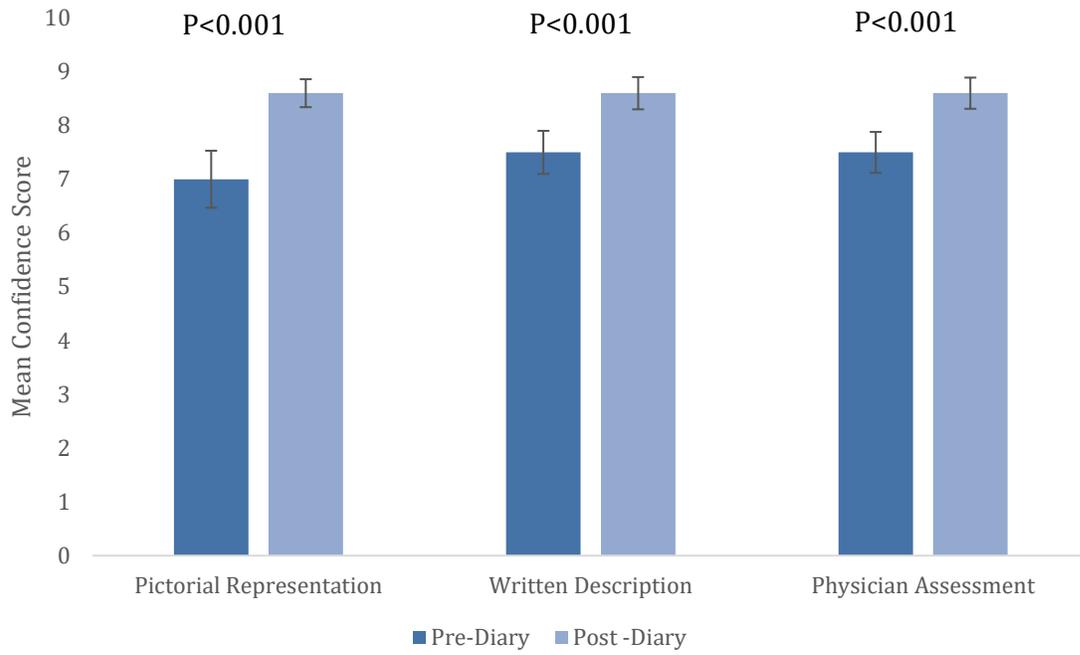
Physician questioning assigned 11/27 (40.7%) as exploding and 16/27 (59.3%) as imploding. Pre-diary vs. post-diary assignment using this method changed for 9/27 (33.3%) patients. The agreement between ascertaining headache directionality at the follow-up visit with diary reporting of headache directionality was 96.2% for the pictorial description (Cohen's kappa = .92 = excellent agreement), 92.3% for the written description (Cohen's kappa = .84 = excellent agreement), and 96.2% for the physician question (Cohen's kappa = .92 = excellent agreement). If the determinations of headache directionality using all three methods were considered together, the directionality that was determined from at least 2 of the 3 methods had 100% agreement with the directionality determined via prospective headache diary entries.

**Table 2:** Cohen’s Kappa values describing inter-rater agreement pre- and post- diary

	Cohen’s Kappa	Cohen’s Kappa
<b><u>Method</u></b>	Initial Visit	Return Visit
<b>Pictorial Representation</b>	0.24	0.92
<b>Written Description</b>	0.38	0.84
<b>Physician Assessment</b>	0.46	0.92

The average confidence that the assignment of directionality was correct pre-diary averaged 7 +/- 2.8 on a scale of 0 (not confident at all) to 10 (completely confident) vs. 8.6 +/- 1.4 post-diary using the pictorial assessment ( $p=.001$ ), 7.5 +/- 2.1 vs. 8.6 +/- 1.6 using the written method of assignment ( $p<.001$ ), and 7.5 +/- 2 vs. 8.6 +/- 1.5 using physician assignment ( $p<.001$ ).

**Table 3:** Confidence scores for each method pre- and post- diary



## Discussion

The main finding of this study is that the ability to determine headache directionality improves after patients prospectively maintain a headache diary that includes self-assessment of headache directionality. There was poor agreement between determination of headache directionality via pictorial assessment, written assessment, and physician question prior to prospective diary keeping with actual headache directionality determined during diary maintenance. However, following diary maintenance all three methods of determining headache directionality had excellent agreement with headache directionality per the gold-standard method of prospective ascertainment. Furthermore, patient and physician confidence in their determination of headache directionality improved following diary maintenance.

The results from this study do not indicate that one method of determining headache directionality is superior to others. The results do suggest that patients are not familiar with the idea of determining their headache directionality during the initial questioning. However, once the topic of headache directionality is introduced and patients prospectively determine their headache directionality during each headache, all three tested methods of determining headache directionality are highly accurate.

The majority of participants in this study reported a combination of imploding and exploding headaches, as opposed to all of their headaches being of one direction. Whether a simple “majority” of headaches being imploding vs. exploding might be indicative of underlying pathophysiology and/or predictive of certain treatment responses or whether a different cut-off would be more appropriate (e.g. 75% one direction or 90% one direction) is not known. Although not systematically captured in this study, some participants reported that they have a change in headache directionality during an individual headache – e.g. the headache starts as imploding and then evolves into an exploding headache. The pathophysiologic and treatment implications of headaches that change direction mid-attack should be further investigated.

Limitations of this study include the relatively small sample size and loss to follow-up. Since study participants maintained a headache diary for only one month, it is not clear that their headaches during that month necessarily represented their typical headaches. It is possible that the ascertainment of headache directionality at the pre-headache diary visit would be more accurate if the results were being compared to the participant's headache directionality over their entire headache history.

## **Future Directions**

Significant findings of this study that warrant future study include the perceived change in headache directionality type experienced within the duration of 1 headache, as described by several patients. Previous studies examining the effects of BTX-A have not made note of this dynamic phenomenon, instead simply classifying patients into the imploding or exploding subtype. Furthermore, one concern the investigators of this study noted is that a 30 day log may not capture the true nature of each patients headaches, particularly in those patients who experience both headache subtypes. As our study only included a 30 day headache log, it would be beneficial to gather data over a longer period of time, perhaps as long as 3-6 months.

## Conclusions

This study analyzed 3 methods of assessing migraine directionality: pictorial representation, written description, and physician assessment. These methods were each conducted at an initial patient visit, and repeated at the follow-up visit. When compared with a 30 day headache log, all 3 initial methods displayed poor agreement. However, all 3 of these methods displayed excellent agreement at the return visit. Furthermore, patients displayed significantly improved confidence in patient ability to determine headache directionality. This suggests that patients have an unfamiliarity with the concepts and terminology of headache directionality, thereby impairing their ability to prospectively identify their own subtype. However, following maintenance of a headache log, patients are much more confident in determining their own headache subtype and at this point, all 3 methods of determination are highly accurate.

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