The Effectiveness of Pharmacological Treatments in Imploding vs. Exploding Headaches in a Women's Health Outpatient Practice

A Thesis submitted to the University of Arizona College of Medicine -- Phoenix
in partial fulfillment of the requirements for the Degree of Doctor of Medicine.

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Class of 2013

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Abstract

Recent research shows variability in the effectiveness of botulinum toxin A among patients who experience their headaches as imploding compared with those who experience exploding headache sensations. Further research has not yet examined whether such variability exists among other pharmacological treatments. This study examines the effectiveness of acute and preventative medications in imploding vs. exploding headaches. 201 patients were recruited in the Women's Health Internal Medicine Program at Mayo Clinic. These patients were given surveys to determine their physician identified headache type (imploding, exploding, or ocular), as well as patient-reported information about the effectiveness of prophylactic medications or triptans. This data was analyzed to determine whether a significant difference existed between medications that were effective for imploding, exploding, or ocular headaches. The study found that no such difference existed. The data was also used to analyze the correlation between physician-identified headache type and the patient-identified headache type. There appears to be only a weak correlation between these assignments, suggesting some room for improvement in the way headache directionality is explored by physician and understood by patients. In the future, research will hopefully uncover additional factors which are useful as predictors for migraine pharmacology.

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Introduction

Migraines are a special class of headaches characterized by severe throbbing, often unilateral pain sometimes associated with nausea, vomiting, photophobia, or phonophobia.[8,9] They affect approximately 12% of the United States population, and represent the most common primary headache disorder in physicians' offices. [11] In addition to causing significant daily impairment for individuals who suffer from them, they are an economic burden causing significant loss of productive time. [7, 9] Their impact on individuals, society, and the medical community have made migraines a prevalent subject of study. Although successful treatment of migraines is difficult due to their unclear etiology, significant progress has been made in the past several decades.

The introduction of triptans – 5-HT1B,D agonists – in the 1990s revolutionized the acute treatment of migraines. Triptans work by targeting the serotonin receptors found along the tregimino-vascular system, inhibiting neurogenic inflammation and causing potent vasoconstriction. Second generation triptans also inhibit trigeminal nerve firing.[9] Despite these advances, there is still a great deal of variability among patient responses, with one study showing over 1/3 of patients do not respond consistently to triptans and less than 50% achieve complete pain freedom. [5]

Medications for migraine prevention suffer from the same inconsistency of effectiveness as do acute treatments. Preventive therapy for migraines is indicated for patients with frequent or disabling attacks, prolonged aura, or poor response to acute therapy. Multiple medications in several classes have long been used for this purpose. For example, amitriptyline, propranolol, topiramate, and divalproex all have similar responder rates and responder therapeutic gains (as judged by a headache severity index) despite their different mechanisms of action. [11] Although studies show similar effectiveness, it is clear from clinical experience that one agent may work or fail for a particular patient without the encouraging data. [12] Likewise, more than 40% of patients do not achieve 50% or better reduction in monthly migraine frequency with valproate and topiramate. [5] The variability among both acute and preventative migraine treatment spurs continuing research in the field of migraine headaches.

In the past decade, migraine research has demonstrated that patients may perceive their pain as pressure buildup inside their head (exploding headache) or as pain inflicted from the outside (imploding headache). Ocular migraines - headaches that involve pressure surrounding the eyes - may also occur, either alone or concurrently with another headache type. Some patients may also experience inter-attack or intra-attack variability between headache types.[4] Most significantly, recent studies suggest that the subjective migraine classification may predict patient responsiveness to an emerging treatment – botulinum toxin A, or Botox. While conducting clinical trials on botulinum toxin type A for the treatment of hyperfunctional facial lines, Binder et al recognized a correlation between pericranial BTX injections and the alleviation of migraine headache symptoms.[1] The toxin produces muscle paralysis by inhibiting presynaptic vesicular release of acetylcholine at the neuromuscular junction. However, its mechanism of migraine prevention is unclear. The success of the botulinum toxin in migraine treatment was also reported by Jakubowski in 2006, and replicated in a retrospective trial by Burstein in 2009.[4, 6] Since the initial studies, however, results were inconsistent in the literature and there was a failure to prove the superiority of botulinum toxin treatments over placebo.

One study by Kim et al. concluded that a possible reason for the inconsistency in treatment outcomes was that all patients with migraines were analyzed together. The study hypothesized that if patients are stratified into groups based on migraine type (imploding, ocular, or exploding), the true response of migraines to treatment could be better recognized. This approach was taken up by a retrospective analysis which examined the success of botulinum toxin in exploding, imploding, and mixed directional headaches, as well as those with and without auras. One hundred twenty-eight patients were identified, and of these patients those with ocular or imploding headache types were most likely to have a >75% reduction in monthly headache frequency. Alternatively, those with exploding or mixed-direction were more likely to be nonresponders. Patients with migraine auras were also more likely to have a >75% reduction in monthly headache frequency than those without auras.[6] A second recent, but much smaller study examined 18 patients who were planning to receive Botox injections for cosmetic purposes. Those with imploding and ocular headaches had significant reductions in

their headache frequency, as opposed to those with exploding headaches who generally did not. Of note, this study examined the dose of Botox used for cosmetic purposes, which is lower than that typically used by headache specialists.[3]

Based on the background provided by previous studies and the increasing awareness of migraine headache directionality, this study will examine the correlation between effective treatments and migraine types. Previous studies have demonstrated both a difference between the pathologies of migraine types and a difference in the response to one treatment, Botox. It stands to reason that these differing pathologies would lead to differing responses to other treatments as well. Utilizing the commonly accepted approach to describing migraine types, patients will be classified according to migraine types and asked to review the effectiveness of both triptans and preventative agents.

Our hypothesis is that there will indeed be some difference in the preventative and triptan treatments for migraines in exploding, imploding, or ocular migraines. If these differences are found, they could help guide treatment selection in the future. Physicians could potentially use the structure of the physician-identified headache type survey to classify patient migraines, and use the identified headache type as a starting point to selecting an appropriate treatment. Positive study results could also provide a basis for further research, such as a double-blind randomized study amongst particular medications or other treatment modalities. Finally, the research would provide additional support to the theory that difference migraine types may have different underlying disease mechanisms.

Research Methods and Materials

The study was carried out with IRB approval through the Mayo Clinic and in compliance with the ethical standards of the Human Subjects Research board. Patients included in the study were female patients who were at least 18 years of age or older. A total of 201 patients were recruited from the Women's Health Internal Medicine department at the Mayo Clinic in Scottsdale, Arizona. The internal medicine clinic was chosen because the large number of patients seen at the clinic presenting with migraines as their chief complaints or as part of their past medical history. Patients included in the study did not need to have migraine headaches as a chief complaint for their visit, but did need to have a current diagnosis of migraines as defined by the Second International Classification of Headache Disorders.

Patients were consented according to research compliance standards. They were then given a patient survey, which included graphic representations of three types of headache pain: exploding (Figure 1a), imploding (Figure 1b), or ocular (see Figure 1c). The basis for these graphical representations comes from a precedent in the migraine literature, in particular previous studies published on botulinum toxin and migraine types (Burstein, et. al. "Migraine prophylaxis with botulinum toxin A is associated with perception of headache" 2009). The surveys also gathered information about patients' current or previous prescription usage – both triptans and prophylactic medications, and the effectiveness perceived by the patient (see Table 1). Demographic information, including age at first migraine and current reproductive status (premenopausal, menopausal transition, menopausal, oophorectomy), was also elicited to determine the baseline characteristics of the study population (see Table 2).

An additional component of the survey was administered by a trained interviewer, including this investigator, and included a series of questions to elicit the physician-identified headache type. Patients could be diagnosed with more than one headache type, having either intra-attack or inter-attack variability. These questions also have a basis in previous studies performed with botulinum toxin, and were chosen with assistance from physicians in the Department of Neurology at Mayo Clinic.

This data was entered in a database by this investigator, and the database was then analyzed by a Mayo Clinic statistician, Dr. Yu-Hui Chang, Ph.D.. Chi-square tests were used to

determine statistical significance between treatment efficacy of patients with and without each migraine type. The medications were analyzed as broad medications classes, as triptans and as prophylactic medications, which is the way they were grouped in the survey. To compare the reliability between two raters, in this case the patient and the physician identification of the patient's headache type, the Kappa inter-rater reliability coefficient was used. This will allow the study to examine whether a patient's categorization of their own headache type aligns with a physician's.

Figure 1: Illustrated depictions of migraine types as portrayed in the patient survey.

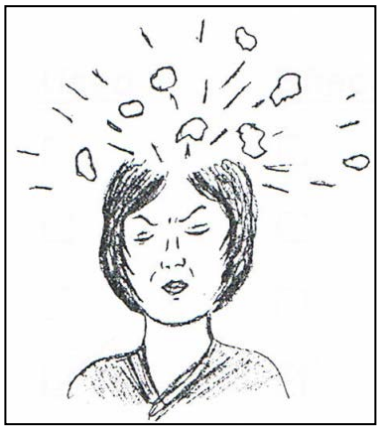

Figure 1a
Exploding Migraine

Figure 1b
Imploding Migraine

Figure 1c
Ocular Migraine

Table 1: Triptan and prophylactic medications from the patient survey

Prophylactic Medications	Triptan Medications
Elavil	Imitrex
Pamelor	Amerge
Inderal	Axert
Topamax	Frova
Depakote	Relpax
Neurontin	Maxalt
Botox	Zomig
Calan	

Table 2: Patient demographic information, n = 201. Some patients did not answer demographic questions.

Menopausal Status	n	%
Reproductive Stage	67	33%
Menopausal Transition	33	16.5%
Postmenopausal	59	29.5%
Hysterectomy w/ ovaries removed before age 50	34	17%

Race / Ethnicity	n	%
White	175	87%
American Indian or Alaska Native	0	0%
Native Hawaiian or Other Pacific Islander	1	0.5%
Black or African American	5	2.5%
Asian	7	3.5%
Other (Hispanic, not otherwise specified)	12	6%

Age	n	%
Younger than 20	3	1.5%
20 – 29	15	7.5%
30 – 39	20	10%
40 – 49	39	19.5%
50 – 59	61	30%
60 – 69	33	16.5%
Older than 70	5	2.5%

Highest Level of Education Attained	n	%
Grade 11 or Lower	4	2%
Graduated High School	6	3%
Some College or Technical School	62	31%
Graduated College	65	32%
Some Graduate Work	15	7.5%
Graduate Degree	48	24%

Age at First Migraine	n	%
Younger Than 10	9	4.5%
10 – 19	85	42%
20 – 29	48	24%
30 – 39	34	17%
40 – 49	16	8%
50 – 59	1	0.5%
Older than 60	1	0.5%

Results

203 patients were initially surveyed. One patient was excluded because the patient was on opioids for another, unrelated condition. A second was excluded because the patient was younger than 18. All other surveys were included in the final analysis. Demographic data was also collected and is reported above in Table 2. The information was not linked to patient identifiers in any way.

A total of 77 patients had used prophylactic agents, and 135 patients had used triptans. These patients were then analyzed based on their physician-identified headache type, and compared to those patients without that headache type, as shown in the tables below (Tables 3, 4, 5). Patients could have more than one headache type and were therefore analyzed within each headache type group into which they were classified. When answering questions regarding specific medications, patients were asked to classify each medication they had tried as either “effective” or “not effective”.

The agreement between physician-identified and patient-identified migraine types was also examined. This was done using an inter-rate reliability study, which examines the extent of the agreement between two raters (the patient and the physician categorizing the patient’s headache type). The Kappa coefficient was used for our analysis. Of note, there was weak to moderate agreement, Kappa coefficient 0.36 ($p<0.0001$), between physician diagnosis of pain directionality and patient self-assignment via answering the written question about pain directionality. There was weak to moderate agreement, Kappa coefficient 0.34 ($p<0.0001$), between physician diagnosis of pain directionality and patient self-assignment via selection of representative pictures. There was weak to moderate agreement, Kappa coefficient 0.35 ($p=0.0005$), between subject self-assignment of pain directionality via answering the written question about pain directionality and choosing from representative pictures.

Imploding Headaches

Table 3a: Imploding headaches, use and effectiveness of prophylactic agents

	w/o imploding headache (n=104)	w/ imploding headache (n=97)	P-value (Chi-square test)
Use of prophylactic agents, n (%)	45 (43.3%)	43 (33.0%)	0.1341
Prophylactive agents were effective, n (%)	32 (71.1%)	19 (59.4%)	0.2832

Table 3b: Imploding headaches, use and effectiveness of triptan agents

	w/o imploding headache (n=104)	w/ imploding headache (n=97)	P-value (Chi-square test)
Use of triptan agents, n (%)	69 (66.4%)	66 (68%)	0.7982
Triptan agents were effective, n (%)	55 (79.7%)	57 (86.4%)	0.3040

Exploding headache

Table 4a: Exploding headaches, use and effectiveness of prophylactic agents

	w/o exploding headache (n=89)	w/ exploding headache (n=112)	P-value (Chi-square test)
Use of prophylactic agents, n (%)	30 (33.7%)	47 (41.2%)	0.2317
Prophylactive agents were effective, n (%)	19 (71.1%)	32 (68.1%)	0.6672

Table 4b: Exploding headaches, use and effectiveness of triptan agents

	w/o exploding headache (n=89)	w/ exploding headache (n=112)	P-value (Chi-square test)
Use of triptan agents, n (%)	56 (62.9%)	79 (70.5%)	0.2535
Triptan agents were effective, n (%)	49 (87.5%)	63 (79.8%)	0.2378

Ocular Headache

Table 5a: Ocular headaches, use and effectiveness of prophylactic agents

	w/o ocular headache (n=101)	w/ ocular headache (n=100)	P-value (Chi-square test)
Use of prophylactic agents, yes n (%)	41 (40.6%)	64 (64%)	0.5029
Prophylactive agents were effective, n (%)	30 (71.1%)	21 (58.3%)	0.1696

Table 5b: Ocular headaches, use and effectiveness of triptan agents

	w/o exploding headache (n=89)	w/ exploding headache (n=112)	P-value (Chi-square test)
Use of triptan agents, yes n (%)	68 (67.3%)	67 (67%)	0.9607
Triptan agents were effective, n (%)	57 (83.8%)	55 (82.1%)	0.7887

Discussion

Based on the study results, there is no significant difference in the use or effectiveness of prophylactic or triptan medications among migraine headache types. This refutes the initial hypothesis, and provides an interesting supplement to previous studies showing a difference when studying Botox treatment. It is possible that the particular mechanism of Botox has varying effectiveness among migraine treatment types, while other medication classes do not. It is also possible that, due to the small sample size of previous Botox studies, no true difference ever existed and this study confirms that migraine directionality does not change the effectiveness of treatment.

With all studies, including this one, the data may suffer from difficulties in patient recall. The surveys ask patient to recall which medications they have used in the past and whether these medications are effective. Some patients may not be able to accurately recall this information. Additionally, the survey may have benefited from some standard definition of effectiveness. As it was, the surveys only asked patients to classify medications as "effective" or "not effective", while asking more particular questions might reveal some medications actually did reduce particular markers, such as frequency, severity, or duration.

The study may have also benefited from a larger sample size. Although there as initially a large patient sample, the proportion of patients using prophylactic and triptan medications was small since not all patients in the study had tried these medications. Additionally some potential differences began to emerge and possibly a larger sample size may have detected these. For example, among patients with imploding migraines, only 59.4% of them found prophylactic agents effective, while 71.1% of patients without imploding migraines found them effective. The p value was 0.2832, and it is possible that with a larger sample size a more significant difference would have been found. Another factor which may have influenced the results was the considerable homogeneity in the patient demographics. For example, the majority of patients are white, between the ages of 40 – 69, and have achieved higher education. These results may have some unforeseen effect on the survey data.

Finally, additional variability may exist in the way in which patients perceive exploding and imploding headaches. Although physicians administer a portion of the survey designed to

diagnose the headache type, patients may have difficulty characterizing their migraines or may not accurately remember the nature of their headaches. Also, the statistical analysis for this study found only a weak correlation between the physician-identified and patient-identified migraine types. Since physician-identified headache type assignments, thought to be more accurate, were used to assign patients to headache type groups, the question remains as to whether patients placed into groups by their self-assigned headache types may have yielded different results. Interestingly, the data also showed weak agreement between patient self-assignment using the illustrations and the written questions, suggesting a flaw with either the illustrative representation or the way in which headache types are described in writing.

The study used the basis of several previous studies[4, 6] which suggested organizing data of responders to various treatment types could be better analyzed by viewing it after separating it according to headache type. Although there were no positive correlations found, this study is important in adding to the growing body of work surrounding migraine research. In particular, it focuses on a new and interesting subject of recent research which suggests a possible difference in treatment responses amongst imploding and exploding headache types.

Future Directions

Although this study does not seem to demonstrate any correlation between headache type and medication use or effectiveness, it still raises interesting questions for future research. A larger study size may offer additional strength to the conclusions of this study. The sample size was not large enough to investigate individual medications, but this could also be an area of further study. Additionally, a more diverse patient population may also be required to create results applicable to a general population. Studies could also examine whether the presence or absence of auras, in addition to directionality, have any effect on which treatment modalities may be effective Alternative therapies, such as Cognitive Behavioral Therapy, relaxation techniques, or herbal treatments may also provide an opportunity to further study migraine directionality. Overall, migraines continue to be a poorly understood and highly prevalent condition in which further research, both proving and refuting hypotheses, will be highly beneficial.

References

1. Binder WJ, Brin MF, et al. Botulinum toxin type A (BOTOX) for treatment of migraine headaches: an open-label study. *Otolaryngol Head Neck Surgery*. 2006; 123: 669-76.
2. Eross EJ, Gladstone JP, Lewis S, Rogers R, Dodick DW. Duration of migraine is a predictor for response to botulinum toxin type A. *Headache*. 2005; 45(4):308- 314.
3. Grogan, PM, Alvarez, MV, Jones L. Headache Direction and Aura Predict Migraine Responsiveness to Rimabotulinumtoxin B. *Headache*. 2013 Jan; 53 (1): 126 – 36.
4. Jakubowski M, McAllister PJ, et al. Exploding vs. imploding headache in migraine prophylaxis with botulinum toxin A. *Pain*. 2006; 125: 286-295.
5. Jamieson, DG. Headache. *Headache*. 2009; 50: 1021- 1030.
6. Kim, Christine MD, Bogart, Megan MD et. al. Predicting migraine responsiveness to botulinum toxin type A injections. *Archives of Dermatology.* Feb 2010; 146: 159-63.
7. Lipton RB, Stewart WF, et al. Prevalence and burden of migraine in the United States: data from the American Migraine Study II. *Headache.* 2001; 41: 646-57.
8. Mathew, NT. Pathophysiology, epidemiology, and impact of migraine. *Clinical Cornerstone.* 2001; 4: 1-17.
9. Mathew NT, Kailasam J, Meadors L. "Predictors of response to botulinum toxin type A (BoNTA) in chronic daily headache." *Headache.* 2008 Feb; 48: 194-200.
10. Ramadan NM and Buchanan TM. New and future migraine therapy. *Pharmacological Therapy.* 2006 Oct; 112: 199-212.
11. Silberstein, SD, Rosenberg J. Multispecialty consensus on diagnosis and treatment of headache. *Neurology.* April 2000 April; 54: 1553.
12. Wheeler, SD. Phenotype-driven preventive strategies for migraine and other headaches. *Neurologist.* March 2009 March; 15: 59-70.