Headache
© 2016 American Headache Society
ISSN 0017-8748
doi: 10.1111/head.12987
Published by Wiley Periodicals, Inc.

Research Submissions

Amitriptyline Dose and Treatment Outcomes in Specialty Headache Practice: A Retrospective Cohort Study

Lauren Doyle Strauss, DO; Emma Weizenbaum, BS; Elizabeth W. Loder, MD, MPH; Paul B. Rizzoli, MD

Objective.—To characterize treatment patterns and real world outcomes in headache patients treated with amitriptyline in an academic headache center.

Design and methods.—A retrospective chart review identified 178 patients in our center who were given a new prescription for amitriptyline in treatment of headache, and who were seen in follow-up within one year. Charts were reviewed to identify dosing patterns (initial and maximum dose) and persistence, patient-reported headache benefit, and reported side effects. Variables assessed in relation to medication use were comorbid psychiatric disease, headache characteristics, and prior use of a preventive medication.

Results.—We followed patients for an average of 6.5 months. Initial and maximum prescribed amitriptyline doses were characterized as: "very low" ($\leq$10 mg daily), "low" (11–25 mg daily), and "traditional" ($\geq$25 mg daily). The initial dose of amitriptyline ranged from 2.5 to 50 mg daily, though most patients were started on a dose of 10 mg daily (112/178, 63%). Approximately 3/4 of the patients were found to have improvement (134/178) and 85% (129/151) were still taking amitriptyline at the last follow-up appointment. Maximum dosing ranged from 2.5 to 100 mg daily with most patients taking 10–25 mg (86/146, 58%). The most commonly reported adverse effect was daytime fatigue (17/151, 11%). There did not appear to be any effect from gender, ethnicity, race, diagnosis of sleep apnea, chronicity of migraine, presence of aura on our outcome measures.

Conclusion.—Our study supports the common clinical practice of using low doses of amitriptyline to treat chronic headache disorders and suggests that it was effective and well tolerated at doses lower than those used in many clinical trials. Use of low dosage amitriptyline may also improve medication persistence, an important clinical consideration in the management of this common and chronic condition. A subgroup of patients may experience a dramatic benefit from amitriptyline and this could warrant further investigation.

Key words: amitriptyline, migraine, prevention, prophylaxis, tolerability, adverse events

(*Headache* 2016;00:00-00)

INTRODUCTION

Amitriptyline, a tertiary amine, has been used in headache prophylaxis since the 1960s, although it is not approved by the United States Food and Drug Administration for this indication.[1] Clinical trial evidence, treatment guidelines, and clinical

From the Pediatric Neurology, Wake Forest Baptist Health Medical Center, Winston-Salem, NC, USA (L.D. Strauss); Department of Neurology, Brigham and Women's Faulkner Hospital, Research Assistant, John R. Graham Headache Center, Boston, MA, USA (E. Weizenbaum); Division of Headache and Pain, Department of Neurology, Brigham and Women's Faulkner Hospital, Boston, MA, USA (E.W. Loder); John R. Graham Headache Center, Department of Neurology, Brigham and Women's Faulkner Hospital, Boston, MA, USA (P.B. Rizzoli).

Address all correspondence to Paul B. Rizzoli, John R. Graham Headache Center, Department of Neurology, Brigham and Women's Faulkner Hospital, 1153 Centre Street, Boston, MA 02130, USA, email: prizzoli@partners.org

Accepted for publication August 29, 2016.

experience support its use.[2-7] Its mechanism of action may involve activity at 5HT (serotonin) receptors.[8] Other postulated mechanisms of action include activity at noradrenaline receptors, sodium channel blockade, and inhibition of descending nociceptive facilitations.[9]

Tricyclic antidepressants, including amitriptyline, show significant efficacy over both placebo and selective serotonin reuptake inhibitor drugs in both migraine and tension-type headache.[10] This meta-analysis also showed that the headache benefit increased with length of use of these medications and, in addition, the reported adverse effects did not influence dropout rates. However, the authors felt that these agents were underused in headache management because of "insufficient understanding of the magnitude of beneficial effects, an overestimation of the adverse effects, or the presumption that efficacy is only confined to migraine headaches."[10] They called for future research to better define effective treatment regimens including target doses, treatment duration, and interactions with abortive or analgesic agents.

Existing clinical trial evidence provides inadequate information about the optimal doses of amitriptyline for headache prophylaxis. In the above meta-analysis,[10] the mean amitriptyline dose across the reviewed studies was 80 mg daily. The balance of benefit to harm ratio of doses below 25 mg per day has rarely been studied.[2,11] Clinical experience suggests that lower doses of amitriptyline are often effective and may be associated with fewer adverse events and improved adherence to treatment.

We therefore sought to characterize clinical outcomes in patients who received various doses of amitriptyline for headache prophylaxis in a tertiary headache clinic. We hypothesized that low (10–25 mg daily), or very low (<10 mg daily) doses of amitriptyline might provide clinical benefit with a more benign side effect profile, in comparison with higher or more traditional doses (>25 mg daily) of the medication.

Conflict of Interest: None.

METHODS

Study Setting and Design.—The Institutional Review Board of Brigham and Women's Hospital, Boston, Massachusetts, approved the study, which was conducted at the adult, multidisciplinary John R. Graham Headache Center. The Center is a tertiary headache referral clinic for Partners Healthcare, which provides care to approximately half of the greater Boston metropolitan area population.[12] We identified unique patients who initiated headache prophylaxis with amitriptyline during a 12-month period beginning July 1, 2011 and extending through June 30, 2012. As background and during the period of the study, roughly 1000 new and 300 follow-up patient visits were made to the clinic. Throughout the study, Partners Healthcare used a proprietary electronic medical record system referred to as the "Longitudinal Medical Record" (LMR). LMR has since been replaced by a different electronic medical record system. LMR collected the same information that is traditionally captured in paper medical records, including demographic information and physician or care provider notes for medical encounters. The LMR also recorded information on prescribed medications, allergies, medical problem lists, and test results. It included prescribing software that allowed clinicians to electronically prescribe medications and other treatments.

We used the "report summary" function in LMR to identify patients at the John R. Graham Headache Center who had started amitriptyline during the study period. We also included a small number of patients who were determined to have started amitriptyline within a month of their first visit to the Center on the recommendation of a clinic physician. Specifically, a search was performed for all prescriptions for "amitriptyline" entered by the five clinic-employed headache specialists who were practicing during the period of the study. One investigator (LS) then searched the individual medical records of all identified patients. Those who had been taking amitriptyline for a long period prior to the first headache clinic visit or who were taking amitriptyline for a reason other than headache during the study period

were excluded. We did not exclude patients for any other reason.

Data Collection.—We created, piloted, and revised a data abstraction form using Research Electronic Data Capture (REDCap). This form is reproduced in Appendix 1. LS abstracted baseline and follow-up visit information from the medical record of eligible patients. She collected information on the following characteristics: (1) principal headache diagnosis assigned by the headache specialist at the visit closest to initiation of amitriptyline, even if that visit had occurred before the study period. Possible categories were migraine, tension-type headache, post-traumatic headache, unknown, or other; we also recorded whether the physician was concerned about medication overuse, even if a formal diagnosis of medication overuse headache was not made; (2) demographic and follow-up information including age, sex, race, ethnicity, number of visits, and interval between initiation and final visits; (3) selected medical and psychiatric comorbidities as identified by physician notation in the chart. Possible categories were sleep apnea, depression, anxiety, post-traumatic stress disorder, eating disorder, obsessive-compulsive disorder, bipolar disorder; (4) currently used headache preventive and abortive medications.

Amitriptyline Treatment Trajectories and Outcomes.—Information was collected on: (1) dose of amitriptyline in milligrams (mg) and by dose category at each visit. Possible categories were very low dose (<10 mg daily), low dose (10–25 mg daily), or traditional dose (>25 mg daily); (2) treatment persistence with amitriptyline. Possible categories were continued, discontinued, or never started. Within the "continued" category we recorded the maximum dose of amitriptyline that had been achieved by the last visit date; (3) adverse effects possibly associated with amitriptyline, as reported in the free text of physician notes; (4) if provided, reasons for discontinuation or failure to begin medication, as reported in the free text of physician notes; and (5) perceived effect of medication on headaches. Possible categories were benefitted, no benefit, or worsened. LS determined the category based on an overall appraisal of documentation in the medical record, including information about any reported changes in headache frequency, intensity or quality, or patient global impression of improvement or reported desire to continue taking amitriptyline. PR reviewed all records. Disagreements were resolved by consensus.

Statistical Analyses.—Data were summarized using descriptive statistics. All statistical analyses were performed using SPSS version 21 (SPSS IBM, Armonk, NY, USA, 2012). Pearson chi-square testing was used to compare categorical values to evaluate for effect modification related to sex, comorbid psychiatric disease, and headache characteristics.

RESULTS

Figure 1 shows the flow of patients through the study. Clinic physicians prescribed amitriptyline for 220 patients during the study period. Forty-two were excluded from the study because they had been taking amitriptyline for over a month at the time the study began, leaving 178 patients whose charts were reviewed in detail. Of those, 27 patients either did not follow-up after starting amitriptyline or follow-up information was not available, leaving 151 patients with documented follow-up. We report these data alone as well as imputing no benefit to all patients without follow-up information.

Table 1 lists the demographic and other characteristics of the study patients. Most were middle-aged Caucasian females with migraine. The average interval from initial to final visit during the one year period was 6.5 months. Medication overuse was mentioned as a possible problem in 8% of patients, likely however not reflective of the true prevalence of this condition.

Initial and Maximum Amitriptyline Doses.—Figure 2 shows the distribution of patients by initial and maximum dose categories. Initial doses of amitriptyline ranged from 2.5 to 50 mg/day. The majority of patients were started on 10 mg/day, and almost 99% of the patients in this study were started on doses in the low or very low dosage range (Table 2). If the prescribing physician decided, based on prior history or patient preference, that a lower dose should be prescribed, we instructed the patient to use ½ or ¼ of a 10 mg

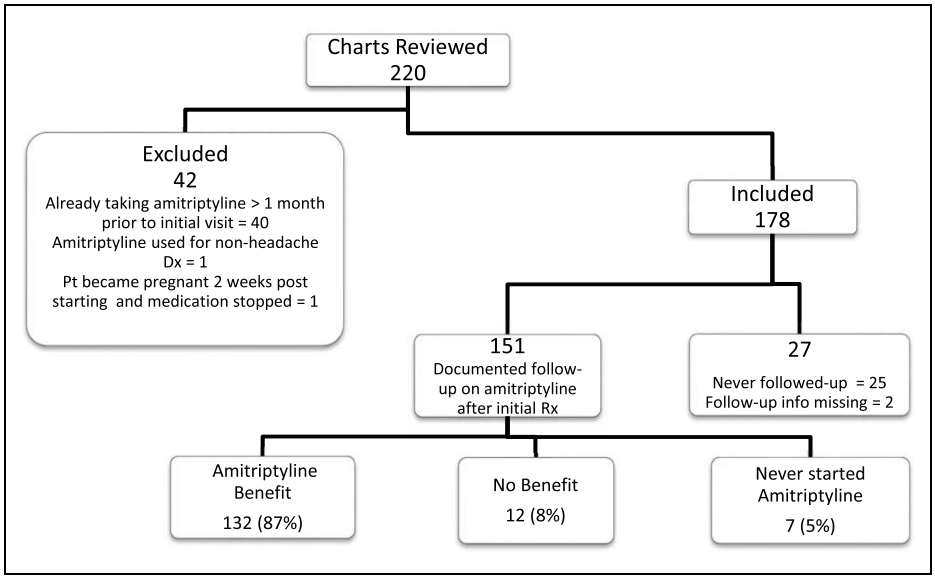

Fig. 1.—Flow chart of study patients.

Table 1.—Characteristics of the Included Patients ($n = 178$)

Age in Years†	
Mean	42.3 (14.7)
Range	18-84
Sex	
Female	137 (77)
Race	
Caucasian	138 (78)
Black	13 (7)
Asian	1 (1)
Unknown/not reported	12 (7)
Ethnicity	
Non-Hispanic	152 (92)
Hispanic	14 (8)
BMI‡	
Mean	27 (5.5)
Range	18-42
Principal headache diagnosis§	178
Migraine	124 (70)
Chronic	78/124 (63)
Aura	34/124 (27)
Tension-type	6 (3)
New daily persistent headache	4 (2)
Post-traumatic headache	13 (7)
Other	21 (12)
Unknown	21(12)
Question of medication overuse	14(8)
Comorbid psychiatric diagnosis	51 (29)
History of sleep apnea	10 (6)

†Data are means (SD) or numbers (%).
‡BMI: Body Mass Index = weight (kg)/height(M)^2.
§Some patients with more than one diagnosis.

tablet to provide a 5 mg or 2.5 mg dose. Actual medication titration rates could not be calculated from the abstracted information; however, a typical practice in the clinic is to change medication dose every 2 weeks if needed.

Seven patients (5%) did not start amitriptyline. Three reported this was due to fear of possible adverse events. One patient experienced headache improvement and decided not to initiate treatment. No reasons were recorded for the other patients.

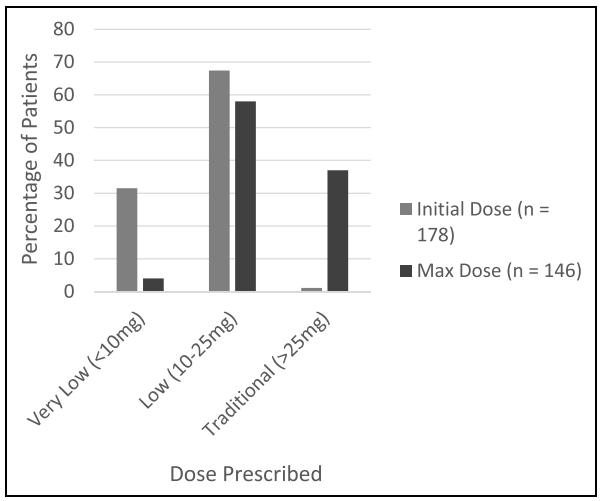

Fig. 2.—Distribution of study patients by initial and maximum dose category.

Table 2.—Initial and Maximum Dose of Amitriptyline (mg Daily)

Dosing Categories	Milligrams/ Day	Initial Doses-Patient # (%) $N = 178$	Maximum Doses-Patient # (%) $N = 146$
Very low dose amitriptyline	2.5 mg	30 (17)	2 (1)
	5 mg	26 (15)	4 (3)
Low dose amitriptyline	10 mg	112 (63)	46 (31)
	15 mg	0	1 (1)
	20 mg	2 (1)	25 (17)
	25 mg	6 (3)	14 (9)
Traditional dose amitriptyline	30 mg	1 (0)	16 (11)
	40 mg		8 (5)
	50 mg	1 (0)	21 (14)
	70 mg		1 (1)
	80 mg		1 (1)
	85 mg		1 (1)
	100 mg		6 (4)

The most common maximum dose in this group (Table 2) was 10 mg ($n = 46$, 31%), and the next most common maximum dose was 20 mg ($n = 25$, 17%). Thus, about half the patients for whom we had data were using a maximum dose of amitriptyline within the range of 10–20 mg daily for headache prevention.

Clinical Impression of Benefit.—Imputing no benefit to those patients who did not follow-up, 132/178 (74%) of patients reported headache benefit while taking amitriptyline. Disagreements in interpretation of the report of benefit in the medical record were resolved by discussion. Excluding from the calculation those for whom no follow-up information was available would result in reported benefit in 132/151 (87%). Three percent of patients (6/178) stopped the medication during the observation period due to lack of benefit.

Dramatic Benefit.—A small proportion of patients who benefitted ($n = 19/132$, 14%), reported dramatic benefit at the time of follow-up. Comments recorded in the patient record such as "changed my life," "have not felt this good in years," "no headache at all," or similar seemed to stand out from other reports of benefit. This group displayed roughly the same demographic features as the total group (data not shown).

In addition, the initial doses in this small group were roughly proportional to those in the larger group (2.5 mg in 26%, 5 mg in 21%, and 10 mg in 53%), except that there were no patients who were started on a dose higher than 10 mg. The maximum dose reached for 63% of this patient group was between 10 and 30 mg daily. Nine patients had a diagnosis of chronic migraine and 3 had episodic migraine.

Adverse Effects.—Twenty-seven percent (41/151) of patients for whom information was available reported one or more adverse effects (Table 3) of which the most common was daytime fatigue (sedation) followed by weight gain. Eleven percent of patients (17/151) reported daytime fatigue. Three percent of patients (5/151) reported weight gain. For those with a comorbid psychiatric disorder there was a trend, 35% (17/48), toward a greater tendency for report of an adverse effect. Twenty-one percent (4/19) of the dramatic benefit group also reported adverse effects. The majority of the patients who started amitriptyline (129/151, 85%) were still taking it at the last follow-up appointment (Fig. 3).

Other Medications.—Fifteen percent of patients (21/141) were taking other daily headache medication(s) at the time amitriptyline was started (Data not shown). Thirty-six percent of these patients were using a concomitant selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine

Table 3.—Adverse Effects of Amitriptyline

Adverse Effect ($N = 151$ Patients)	N (%)
Daytime fatigue	17 (11)
Weight gain	5 (3)
Dry mouth	2 (1)
Mood change	2 (1)
Lightheadedness	2 (1)
Cognitive complaints	2 (1)
Other: tongue pain (1), tinnitus (1), jittery (1), formication (1), blurred vision (1), unsteadiness (1), constipation (1)	11 (7)

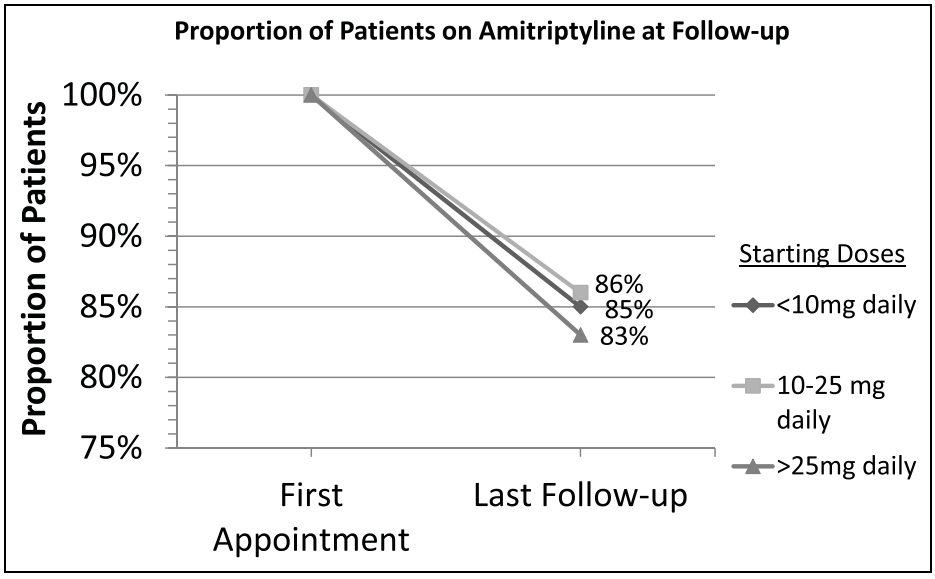

Fig. 3.—Medication persistence of amitriptyline.

reuptake inhibitor (SNRI) drug. Other concomitant medications in use included topiramate (20%), a beta blocker (14%), a calcium channel blocker (12%), gabapentin (9%), and an angiotensin-converting enzyme (ACE) inhibitor (9%)

Comorbid Conditions.—We searched for the following comorbid conditions in this patient group: sleep apnea, anxiety, depression, post-traumatic stress disorder, eating disorder, and obsessive compulsive disorder. Of these, the most commonly reported comorbid conditions were anxiety and depression (each: $n = 33/178$, 17%). The study was not large enough to further evaluate these possible effect modifiers.

DISCUSSION

This real-world retrospective cohort study of 178 patients started on amitriptyline for headache prevention in a tertiary headache center examined the outcome measures of patient impression of benefit, dosing, and persistence and adverse effects.

The patient-reported outcome measure of amitriptyline benefit for headache was used, as reflected in the chart notes. This measure of treatment benefit, how the patient feels and functions, though imprecise, is increasingly used[13] and has the advantage of reflecting a patient's overall estimation of the balance of benefits and harms from a treatment. Further, such a measure may be particularly valuable in the assessment of treatment benefit in chronic conditions where the goal is amelioration of symptoms and maintenance of function rather than cure.[14] With this measure we showed significant benefit from amitriptyline at relatively low maximal dosage, suggesting that initiation of amitriptyline at "traditional" doses may miss a low dosage treatment effect and could engender adverse effects of a severity that may compromise treatment. That a small number of patients responded particularly strongly to amitriptyline is an interesting sidelight that could warrant more scrutiny. Other migraine-preventive medications have also been reported beneficial at low dosage.[15,16]

Though most patients in this study took 10-20 mg daily, some patients used as little as 2.5 mg daily and others as much as 100 mg daily, and guidelines[17] have noted that a wide range of amitriptyline doses may be effective. Why is there such a wide range of apparently effective amitriptyline doses? One explanation could be genetic differences in drug metabolism. Amitriptyline is metabolized in the cytochrome system, mainly by CYP2D6,[18] which is responsible for the oxidative metabolism of up to 25% of commonly prescribed drugs. This gene is highly polymorphic with 70 alleles and 130 genetic variations.[19-21] Four

phenotypic groups have been identified for CYP2D6: 2-15% of all patients are poor metabolizers with 2 null alleles and thus absent enzymatic activity.[22] This includes 5-10% of the Caucasian population, but is rare in Asians and variable in those of African ancestry; intermediate metabolizers (2-11% of patients) with either a null allele along with a functioning allele or two deficient alleles; extensive metabolizers (77-92% of patients) with at least one functional allele; and ultrarapid metabolizers (1-2% of patients) who carry duplicate functional alleles. Characterization of the metabolic status of patients is not routinely carried out in clinical practice. Serum amitriptyline levels, though not in wide use in headache management, could presumably provide clues as to the patient's ability to metabolize the drug.

In our study a substantial number of patients, 85%, were still taking amitriptyline at their last follow-up visit at an average of about 6 months out (Fig. 3). Prior studies have shown much lower persistence, 55% at 16-26 weeks in one[23] and 13% at 6 months in another.[24] Our results suggest that amitriptyline may be more beneficial and well tolerated than commonly suspected. The possibility of development, 1-2 years out, of tolerance/tachyphylaxis to amitriptyline could not be assessed in this study due to its shorter duration.

Adverse effects were the most common reason for avoiding or discontinuing amitriptyline. Sedation, or daytime fatigue, is probably the major reported adverse effect from tricyclic medications[25] and may be due to antimuscarinic effects (sedation, blurred vision, dry mouth, constipation, urinary retention) with a role for antihistamine effects as well. Our data failed to show an expected association between the dose of amitriptyline and the likelihood of reporting adverse events. Adverse events appeared to be about as common in patients receiving very low or low initial doses of medication. We did not observe any evidence of tolerance or tachyphylaxis to the clinical effects of amitriptyline, phenomena that have previously been reported with some drugs and which may be due to a number of causes and mechanisms.[26,27] It is plausible that treating physicians chose to start patients on very low or low doses of amitriptyline if they perceived, based on patient characteristics, that a particular patient might be very prone to adverse effects. Treatment persistence, however, was still quite high in these "very low" and "low" dosing groups despite reported adverse events.

Our study has both strengths and limitations. This study was uncontrolled and for hypothesis-generating purposes. The study lacked blinding, a control group, validated pain scores, headache journal documentation, and was open to bias both on the part of the provider and in the interpretation of their medical record entries. Adverse effects were not systematically sought or recorded during office visits, almost certainly resulting in an underestimate of their occurrence. More severe adverse effects, however, were likely both reported and recorded. The study does provide a strong clinical impression of benefit for low and very low dose amitriptyline in multiple headache types. This impression could be tested further in a controlled, randomized, blinded fashion.

CONCLUSION

Our study supports the common clinical practice of using low doses of amitriptyline to treat chronic headache disorders,[28] and suggests that it was effective and well tolerated at doses lower than those used in many clinical trials. Use of low dosage amitriptyline may also improve medication persistence, an important clinical consideration in the management of this common and chronic condition. A subgroup of patients may experience a dramatic benefit from amitriptyline and this could warrant further investigation.

Acknowledgments: This work was conducted with support from Harvard Catalyst/The Harvard Clinical and Translational Science Center (National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health Award UL1 TR001102) and financial contributions from Harvard University and its affiliated academic healthcare centers. The content is solely the responsibility of the authors and does not necessarily represent the official views of Harvard Catalyst,

Harvard University and its affiliated academic healthcare centers, or the National Institutes of Health.

STATEMENT OF AUTHORSHIP

Category 1

(a) Conception and Design
Paul B. Rizzoli, Lauren Doyle Strauss, Elizabeth W. Loder

(b) Acquisition of Data
Lauren Doyle Strauss

(c) Analysis and Interpretation of Data
Lauren Doyle Strauss, Emma Weizenbaum, Paul B. Rizzoli

Category 2

(a) Drafting the Manuscript
Lauren Doyle Strauss, Paul B. Rizzoli

(b) Revising It for Intellectual Content
Paul B. Rizzoli, Elizabeth W. Loder

Category 3

(a) Final Approval of the Completed Manuscript
Paul B. Rizzoli

REFERENCES

1. Lance JW, Curran DA. Treatment of chronic tension headache. *Lancet.* 1964;1:1236-1239.
2. Gomersall JD, Stuart A. Amitriptyline in migraine prophylaxis. Changes in pattern of attacks during a controlled clinical trial. *J Neurol Neurosurg Psychiatry.* 1973;36:684-690.
3. Ziegler DK, Hurwitz A, Hassanein RS, Kodanaz HA, Preskorn SH, Mason J. Migraine prophylaxis. A comparison of propranolol and amitriptyline. *Arch Neurol.* 1987;44:486-489.
4. Ziegler DK, Hurwitz A, Preskorn S, Hassanein R, Seim J. Propranolol and amitriptyline in prophylaxis of migraine. Pharmacokinetic and therapeutic effects. *Arch Neurol.* 1993;50:825-830.
5. Loder E, Burch R, Rizzoli P. The 2012 AHS/AAN guidelines for prevention of episodic migraine: A summary and comparison with other recent clinical practice guidelines. *Headache.* 2012;52:930-945.
6. Dodick DW, Freitag F, Banks J, et al. Topiramate versus amitriptyline in migraine prevention: A 26-week, multicenter, randomized, double-blind, double-dummy, parallel-group noninferiority trial in adult migraineurs. *Clin Ther.* 2009;31:542-559.
7. Couch JR. Amitriptyline Versus Placebo Study Group. Amitriptyline in the prophylactic treatment of migraine and chronic daily headache. *Headache.* 2011;51:33-51.
8. Goadsby PJ. How do the currently used prophylactic agents work in migraine? *Cephalalgia.* 1997;17:85-92.
9. Welch KM. Contemporary concepts of migraine pathogenesis. *Neurology.* 2003;61:S2-S8.
10. Jackson JL, Shimeall W, Sessums L, et al. Tricyclic antidepressants and headaches: Systematic review and meta-analysis. *BMJ.* 2010;341–354:c5222.
11. Diamond S, Baltes BJ. Chronic tension headache-treated with amitriptyline–A double-blind study. *Headache.* 1971;11:110-116.
12. Partners HealthCare®. Available at: http://www.partners.org/About/History-Achievements/History-of-Partners.aspx. Accessed May 11, 2016.
13. Zagadailov E, Fine M, Shields A. Patient-reported outcomes are changing the landscape in oncology care: Challenges and opportunities for payers. *Am Health Drug Benefits.* 2013;6:264-274.
14. Gnanasakthy A, Mordin M, Clark M, DeMuro C, Fehnel S, Copley-Merriman C. A review of patient-reported outcome labels in the United States: 2006 to 2010. *Value Health.* 2012;15:437-442.
15. Linde M, Mulleners WM, Chronicle EP, McCrory DC. Valproate (valproic acid or sodium valproate or a combination of the two) for the prophylaxis of episodic migraine in adults. *Cochrane Database Syst Rev.* 2013 Jun 24;(6):CD010611.
16. Deaton TL, Mauro LS. Topiramate for migraine prophylaxis in pediatric patients. *Ann Pharmacother.* 2014;48:638-643.
17. Pringsheim T, Davenport W, Mackie G, et al. Canadian Headache Society guideline for migraine prophylaxis. *Can J Neurol Sci.* 2012;39:S1-S59.
18. Samer CF, Lorenzini KI, Rollason V, Daali Y, Desmeules JA. Applications of CYP450 testing in the clinical setting. *Mol Diagn Ther.* 2013;17:165-184.
19. Ingelman-Sundberg M, Oscarson M, McLellan RA. Polymorphic human cytochrome P450 enzymes: An opportunity for individualized drug treatment. *Trends Pharmacol Sci.* 1999;20:342-349.
20. Bertilsson L, Dahl ML, Dalen P, Al-Shurbaji A. Molecular genetics of CYP2D6: Clinical relevance

with focus on psychotropic drugs. *Br J Clin Pharmacol.* 2002;53:111-122.
21. Steimer W, Zopf K, von Amelunxen S, et al. Amitriptyline or not, that is the question: Pharmacogenetic testing of CYP2D6 and CYP2C19 identifies patients with low or high risk for side effects in amitriptyline therapy. *Clin Chem.* 2005; 51:376-385.
22. Hicks JK, Bishop JR, Sangkuhl K, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 and CYP2C19 genotypes and dosing of selective serotonin reuptake inhibitors. *Clin Pharmacol Ther.* 2015;98:127-134.
23. Hepp Z, Bloudek LM, Varon SF. Systematic review of migraine prophylaxis adherence and persistence. *J Manag Care Pharm.* 2014;20:22-33.
24. Yaldo AZ, Wertz DA, Rupnow MF, Quimbo RM. Persistence with migraine prophylactic treatment and acute migraine medication utilization in the managed care setting. *Clin Ther.* 2008;30:2452-2460.
25. Silberstein SD, Goadsby PJ. Migraine: Preventive treatment. *Cephalalgia.* 2002;22:491-512.
26. Loder EW, Rizzoli P. Tolerance and loss of beneficial effect during migraine prophylaxis: Clinical considerations. *Headache.* 2011;51:1336-1345.
27. Rizzoli P, Loder EW. Tolerance to the beneficial effects of prophylactic migraine drugs: A systematic review of causes and mechanisms. *Headache.* 2011;51:1323-1335.
28. Couch JR, Ziegler DK, Hassanein RS. Evaluation of amitriptyline in migraine prophylaxis. *Trans Am Neurol Assoc.* 1974;99:94-98.