Systematic Review of Migraine Prophylaxis Adherence and Persistence

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ABSTRACT

BACKGROUND: Migraine is a common neurological disease affecting 12% of Americans and millions worldwide. Medication adherence has been studied extensively in many chronic conditions, with poor adherence adversely affecting treatment outcomes. However, little is known about adherence to oral prophylaxis for migraine.

OBJECTIVE: To examine the literature on assessing oral prophylaxis medication adherence and persistence among migraine patients.

METHODS: A systematic search of the PubMed (1966 to present) and EMBASE (1974 to present) databases was conducted to locate prospective and retrospective observational studies and randomized controlled trials (RCTs) of propranolol, amitriptyline, and topiramate. RCTs were pooled, weighted by sample size, and stratified by drug and length of study. Average persistence rates and reasons for discontinuation cited in RCTs were examined for each medication.

RESULTS: A total of 788 unique articles were identified using the search criteria, 33 of which were included in the final review. Observational studies (n = 14) showed adherence ranges of 41% to 95% at 2 months, 21% to 80% at 6 months, and 35% to 56% at 12 months and persistence ranges of 41% to 88% at 2 months, 19% to 79% at 6 months, and 7% to 55% at 12 months. Pooled persistence from RCTs on propranolol, amitriptyline, and topiramate (n = 19) showed rates of 77%, 55%, and 57%, respectively, at 16-26 weeks. Adverse events were the most common reason for discontinuation cited (24% for topiramate and 17% for amitriptyline).

CONCLUSION: Observational studies and pooled data from RCTs demonstrate poor adherence and persistence to oral migraine prophylaxis.

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What is already known about this subject

- Adherence measures provide a basic method for quantifying the extent to which patients follow a prescribed therapy over a specified time period. Generally, adherence is determined by calculating a ratio of doses taken on schedule compared with the total number of doses prescribed, while persistence is a measurement of the time during which a patient remains on a prescribed medication after initiating therapy.
- Chronic therapies are generally associated with poor adherence (<80% of medication taken as prescribed), which has been linked to poor outcomes. This lack of adherence has been demonstrated by large systematic literature reviews in various chronic conditions such as type 2 diabetes, hypertension, and osteoporosis. At the time of this review, no systematic literature reviews have been published on adherence or persistence to migraine prophylactics.

What this study adds

- This comprehensive review of the literature showed that migraine prophylactics are associated with poor adherence and persistence. This is the first such literature review for this class of medication.
- This review is the first to include both observational studies and RCTs and to incorporate various methods for presenting adherence and persistence measures. It provides a summary of a wide range of data available on adherence and persistence related to migraine prophylaxis.

Migraine is a neurological condition that affects approximately 12% of patients in the United States and millions worldwide.¹ Women are affected disproportionately, with a 3-fold higher prevalence of migraine disorder. Prevalence peaks between age 25 and 55 years, affecting the most productive years of a person's life.² Patients experience varying levels of frequency, severity, and disability associated with migraine. More frequent and severe cases with significant impact on patients' quality of life and daily activities may benefit from headache prophylaxis. Existing prophylaxis therapies include a variety of options (e.g., beta blockers, antidepressants, anticonvulsants, onabotulinumtoxinA). At the time of this study, guidelines, such as those published by the U.S. Headache Consortium, recommended first-line prophylaxis with propranolol, timolol, amitriptyline, or divalproex.³ Although some patients see relief from these therapies, unfavorable side effects may limit tolerability and thus impact the effectiveness of prophylaxis. Ultimately, patient tolerance is a crucial component for the success of migraine prophylaxis. A study that explored the extent to which migraine patients are willing to tolerate side effects of prophylaxis found that the top reasons why a prophylactic is deemed intolerable to patients are weight gain, memory loss, depression, and somnolence.⁴ These findings can be readily applied to migraine prophylaxis, where possible side effects include cognitive effects (topiramate), somnolence (amitriptyline and propranolol), and weight gain (divalproex).

Adherence refers to the extent to which a patient follows prescribed directions with respect to timing, dose, and frequency.⁵ Adherence to chronic therapy is a common issue across many disease states. Poor adherence (<80% of medication taken as prescribed) has been associated with poor outcomes in a number of medication classes.⁶⁻¹⁰

FIGURE 1 Results of Systematic Review (PubMed 1966-Present and EMBASE 1974-Present)

Medication adherence is often determined by a ratio of doses taken on schedule compared with the total number of doses prescribed over a specified period.¹¹ In observational studies, this ratio can be determined through pill counts conducted by an investigator or logged by a medication event monitoring system (MEMS). Pill counts provide an accurate measure of adherence by comparing the prescribed quantity of drug with the actual quantity of drug taken by the patient over a period of time. MEMS has the additional benefit of providing an electronic time stamp that measures whether the drug is taken at the prescribed dosage interval.¹² Another way to determine adherence is by calculating the medication possession ratio (MPR) or proportion of days covered (PDC) using pharmacy claims data. MPR is the sum of the days supply for all fill periods divided by the total number of days in that period. PDC is calculated as the number of days with drug on hand divided by the number of days in the specified time interval.¹³ MEMS is considered perhaps the most precise measure of adherence

because it captures both quantity and dosage interval; however, claims database analyses and patient-reported adherence remain the most common methodologies employed due to the ability of conducting large studies quickly and at relatively low cost.^{14,15}

Persistence refers to the time during which a patient remains on a prescribed medication after initiating therapy. While persistence can be measured directly by patient questionnaires and claims analyses, it may also be measured indirectly from discontinuation rates reported in observational and randomized controlled trials (RCTs).¹¹ While RCTs employ a structured program of care that may result in low discontinuation rates compared with the real-world patient experience, trends of discontinuation over time, as well as reasons for discontinuation reported in RCTs, may yield important information on persistence.

Many comprehensive literature reviews have been conducted on the adherence and persistence to chronic

Systematic Review of Migraine Prophylaxis Adherence and Persistence

TABLE 1 Observational Studies on Oral Migraine Prophylaxis Adherence and Persistence

Reference	N	Design	Study Country	Outcome Measure	Time Horizon (Weeks)	Treatment	Mean Age	% Female	Headache Frequency (Days/Month)	Results
Gaul 2011 ¹⁶	295	PRO, PI	Germany	Adherence (self-reported: headache diary and phone interview)	80	Topiramate, beta blockers, magnesium, amitriptyline, flunarizine, tizanidine, opipramol, duloxetine, valproate, butterbur, and lamotrigine (any dose of each)	41	88.8	Tension headache 27 (4-30); migraine 11 (1-30); tension + migraine 18 (2-30)	91% adherent at first fill, 39% at 5 months, and 35% at 12-18 months
Heckman 2011 ¹⁷	109	PRO, PI	USA	Adherence (self-reported: headache diary)	4	Antidepressants, anticonvulsants, beta blockers, calcium blockers, and other (non-steroidal, low-dose aspirin, Botox) (any dose of each)	39	90.5	17 ± 7.7	78% adherent at 1 month (reported separately as 69% for African-American patients and 82% for Caucasian patients)
Berger 2009 ²⁰	5,187	RET, CD	USA	Adherence (claims-based MPR)	24	All tricyclics and SSRI antidepressants, bupropion, mirtazapine, trazodone, venlafaxine, carbamazepine, divalproex, gabapentin, topiramate, atenolol, metoprolol, nadolol, propranolol, and timolol (any dose of each)	N/A	N/A	N/A	92.6% adherent at 1 month, 40.7% at 2 months, 30.9% at 3 months, 24.8% at 4 months, 24.3% at 5 months, 20.8% at 6 months
Lafata 2010 ¹⁹	2,517	RET, CD	USA	Adherence (claims-based MPR)	56	Amitriptyline, venlafaxine, fluoxetine, carbamazepine, gabapentin, topiramate, prinzivil, lisinopril, candesartan, nifedipine, diltiazem, verapamil, metoprolol, atenolol, inderal, propranolol, and timolol (any dose of each)	40	77	N/A	56% adherent at 12 months
Rothrock 2006 ¹⁸	41	PRO, SURV	USA	Adherence (self-reported: headache diary)	24	Anticonvulsants: divalproex, topiramate, zonisamide, or gabapentin (any dose of each)	42.5	92	Mean 18 (SD N/A)	Received patient education, 96% adherent at 6 months; no education, 58.5% adherence at 6 months; composite 79% at 6 months
Mulleners 1998 ¹²	38 (11 lost to follow-up)	PRO, SURV	United Kingdom	Adherence (pill count and MEMS)	8	Propranolol 160 mg qd, atenolol 50 mg bid, pizotifen 0.5 mg, or methysergide 1 mg tid	N/A	75.9	Mean or median N/A, range 2-8	66.1% adherent at 2 months (79.8% for once daily, 60% for twice daily, and 54.2% for 3 times daily dosing)
Yaldo 2008 ²⁸	12,783	RET, CD	USA	Persistence (Kaplan-Meier analysis of claims database)	N/A (until discontinuation)	Amitriptyline, propranolol/timolol, divalproex sodium, and topiramate (any dose of each)	42-43.9	83.9	N/A	92.4% persistent at 1 month, 41.0% at 2 months, 31.4% at 3 months, 25.2% at 4 months, 21.3% at 5 months, 18.5% at 6 months, 11.5% at 9 months, 7.3% at 12 months

TABLE 1 Observational Studies on Oral Migraine Prophylaxis Adherence and Persistence (*continued*)

Reference	N	Design	Study Country	Outcome Measure	Time Horizon (Weeks)	Treatment	Mean Age	% Female	Headache Frequency (Days/Month)	Results
Krymchantowski 2011 ²⁵	120	MC, PRO, COM, OL	Brazil	Discontinuation (headache diary)	12	Divalproex sodium 500 mg bid vs. topiramate 75 mg bid	41.2	86.6	8 ± 4	65.8% persistent at 3 months
Nelles 2010 ²¹	332	PRO, MC, OL, NIS	Germany	Discontinuation (reported as part of primary outcome for tolerability)	56	Topiramate 25-200 mg	41.8	76.9	N/A	77.7% persistent at 6 months, 60.4% at 9 months, 54.5% at 12 months
Malessa 2010 ²²	364	PRO, MC, OL, SA	Germany	Discontinuation (secondary outcome measure in open-label study)	24	Topiramate 50-200 mg	43.7	87.8	Mean 8.84 (SD 3.28); median 8 (range 1-24)	62.4% persistent at 6 months, 41.3% at 12 months
Lampl 2009 ²⁴	150	PRO, MC, OL	Austria	Discontinuation (secondary outcome measure in open-label study)	24	Amitriptyline ER 25-50 mg qd	32	73	Median 7 (range 4-14)	88.0% persistent at end of 2 months titration period, 81.3% at 1 month (total 3 months), 76.0% at 3 months (total 6 months)
Mei 2004 ²³	185	PRO, MC, OL	Germany	Discontinuation (secondary outcome measure in open-label study)	24	Topiramate 100-200 mg qd	45.7	90.7	Mean 6.2 (SD 3.9); median 6 (range 0-23)	75% persistent at 1 month, 65% at 3 months, 59% at 6 months
Rahimtoola 2003 ²⁷	729	RET, CD	Netherlands	Discontinuation (Kaplan-Meier analysis of claims database)	N/A	Propranolol, metoprolol, pizotifen, methysergide, flunarizine, clonidine, valproic acid (any dose of each)	40	80.8	N/A	48% persistent at 3 months, 34% at 6 months, 23% at 12 months
Verspeelt 1996 ²⁶	1,601	PRO, MC, COM	Belgium	Discontinuation (doctor surveys)	32	Flunarizine 5-10 mg qd, propranolol 40-320 mg qd	41	76.5	N/A	65.3% persistent at 1 month, 50.6% at 4 months, 40.6% at 8 months

bid = twice daily; CD = claims database; COM = comparative; FD = fixed dose; MC = multicenter; MEMS = medication event monitoring system; mg = milligram; MPR = medication possession ratio; N/A = not available; NIS = noninterventonal study; OL = open label; PI = phone interview; PRO = prospective; qd = once daily; RET = retrospective; SA = single arm; SD = standard deviation; SSRI = selective serotonin re-uptake inhibitor; SURV = survey; tid = 3 times daily.

medications; however, none have been published on migraine prophylaxis to date. The purpose of this systematic literature review is to summarize all available evidence of adherence and persistence to 3 common oral medications used as migraine prophylaxis.

Methods

Search Methods

Potential studies were identified by searching the PubMed (1966 to July 1, 2011) and EMBASE (1974 to July 1, 2011) databases for “migraine prophylaxis” combined with the terms “adherence” OR “compliance” and “migraine prophylaxis” combined with each of the following medications: “propranolol” OR “amitriptyline” OR “topiramate” (Figure 1). The medications chosen for this review are the 3 most commonly used oral medications for migraine prophylaxis, and each is

a member of a major therapeutic class of oral agents used as migraine prophylaxis (beta blockers, antidepressants, and anticonvulsants). Studies were limited to prospective and retrospective observational studies on adherence and persistence of migraine prophylaxis and RCTs of the 3 aforementioned migraine prophylaxis medications. Studies examining use for headache disorders other than migraine were excluded, as were editorials/commentaries, reviews, case studies, animal studies, cost-effectiveness studies, pharmacokinetic studies, and guidelines. Articles not available in English and studies conducted in children/adolescents (< 18 years of age), elderly, and pregnant subpopulations were also omitted.

Data Synthesis

Observational studies and RCTs were analyzed separately. Adherence and persistence data from observational studies were

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TABLE 2 Persistence Data from Randomized Controlled Trials of Oral Migraine Prophylaxis

Reference	N	Design	Study Country	Inclusion Criteria	Exclusion Criteria	Study Length (Weeks)	Treatment	Baseline Headache Frequency Mean (SD)	Age Mean (SD) or Median (Range)	% Female	Discontinuation Rates (%)
Mohammadianinejad 2011 ³¹	80	DB, PC, RCT	Iran	Dx of migraine defined by IHS for 1 yr, 4-15 migraines per month, failed 1 or more prophylactics, 1 yr after menopause if menopause already occurred, negative pregnancy test and appropriate contraceptive use during the study	Dx of any other HA or pain, pregnancy, prior use of study medication	12	Topiramate 100 mg qd	3.7 (1.89)	35.5 (9.5)	77.5	5
							Zonisamide 200 mg qd	3.6 (1.42)	33 (9.2)	80	7.5
Cady 2011 ³²	59	MC, DB, RCT	USA	18-65 yrs w/Dx of CM defined by IHS 2nd ed., 3-8 migraine attacks per month with avg. 21 HA days, negative pregnancy test	Pregnant or breastfeeding, Dx w/other HA besides chronic migraine, renal or liver impairment, previous use of study medication, ketogenic diet, alcohol/drug abuse, or overuse of acute medications	12	Topiramate 100-200 mg qd	20.5	39.6 (19.6-64)	91.5	26.7
							OnabotulinumtoxinA 100-200 units injection	21.8			24.1
Couch 2010 ³³	391	MC, DB, PC, RCT	USA	18-70 yrs w/Dx of migraine as defined by the 1962 Ad Hoc National Institutes of Health Committee and the 1988 ICHD Guidelines with at least 2 moderate or worse migraines per month	Secondary HA, pregnant or nursing mothers, urinary retention, glaucoma, cardiac disease, sustained hypertension, concurrent guanethidine or MAOIs, prostate hypertrophy, thyroid disease, concurrent thyroid medications, seizure disorders, current anti-migraine agent or known hypersensitivity to study medication	20	Amitriptyline 25-100 mg qd	N/A	34.1	79	48
							Placebo qd		34.0	83	54
Rodriguez-Leyva 2010 ³⁴	36	DB, COM, RCT	Mexico	18-60 yrs w/Dx of migraine defined by IHS at least 6 months prior to study start date and before age 40 with 3 or more migraine events per month	Pregnancy or lactation, Dx of other HA, history of renal lithiasis, glaucoma, schizophrenia, bipolar disorder, infectious, immunologic, cardiovascular, prostatic, or metabolic disease, known hypersensitivity to study medication	16	Amitriptyline 25-50 mg qd	N/A	31.6 (9.6)	88.9	27.8
							Topiramate 25-50 mg qd	N/A	36.3 (10.5)	83.3	22.2
Domingues 2009 ³⁵	76	DB, COM, RCT	Brazil	> 18 yrs w/Dx of migraine or chronic migraine defined by IHS 2nd ed. with 4 or more attacks of migraine per month. No prior or current use of a prophylactic was allowed	Bronchial asthma, symptomatic hypotension, hyperlactemia, bladder retention, known hypersensitivity to study medication	12	Propranolol 40 mg bid	N/A	N/A	N/A	44
							Nortriptyline 20 mg bid	N/A	N/A	N/A	42
							Propranolol 40 mg + nortriptyline 20 mg bid	N/A	N/A	N/A	41
Dodick 2009 ³⁶	331	MC, DB, COM (NI), RCT	USA	≥ 18 yrs w/Dx of migraine defined by IHS for at least 6 months and 3-12 (but not more than 15) migraines per month for 3 months prior to study date	Previously failed > 2 trials of migraine preventative medication (trial lasting ≥ 3 months) or had failed trial of topiramate or amitriptyline because of a lack of efficacy or adverse event, using abortive HA medication for > 15 days per month, onset of migraine after age 50, other type HA, contraindication to study medications, unstable medical condition in the last 2 yrs, psychiatric disorder in the last 6 months, drug or alcohol abuse, liver disease, pregnant or nursing, not practicing birth control	26	Topiramate 50 mg bid	6.1 (2.7)	39.7 (10.7)	86.6	40.7
							Amitriptyline 100 mg qd	6.2 (2.7)	37.9 (11.3)	83	40.3

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TABLE 2 Persistence Data from Randomized Controlled Trials of Oral Migraine Prophylaxis (continued)

Reference	N	Design	Study Country	Inclusion Criteria	Exclusion Criteria	Study Length (Weeks)	Treatment	Baseline Headache Frequency Mean (SD)	Age Mean (SD) or Median (Range)	% Female	Discontinuation Rates (%)
Adelman 2008 ³⁷	1,580	PD from pivotal DB, PC, RCT	USA	12-65 yrs w/Dx of migraine with or without aura defined by IHS at least 6-12 months prior to study start date with 3-12 (but no more than 15) migraine events per month during 1 month prior to study, postmenopausal or practicing birth control	Dx for another type of HA, migraine started after age 50, failed 2 or more doses of migraine prophylactic, overuse of analgesics, triptans, or other acute migraine treatments, concomitant prophylactic, diagnosed and treated depression 3 months prior to study start date, nephrolithiasis, participants of previous topiramate or other experimental study 30 days prior to screening	20-26	Topiramate 50 mg qd	N/A	39.5 (11.8)	87	46
							Topiramate 100 mg qd	N/A	39.9 (11.4)	86	38
							Topiramate 200 mg qd	N/A	40.5 (11.8)	85	46
							Placebo qd	N/A	40.1 (10.9)	83	35
Ashtari 2008 ³⁸	62	DB, COM, RCT	Iran	12-65 yrs w/Dx of migraine with or without aura defined by IHS at least 1 yr prior to study start date with 3 or more migraine events per month during 3 months prior to study, onset < 50 yrs of age, pain free interval of 48 hours between attacks, concomitant prophylactics discontinued 1 month prior to entry into trial	Pregnant or breast feeding, concomitant medical condition including renal stones, cardiac, liver, or neoplastic diseases, and neurologic disorders	8	Topiramate 50 mg qd	6.07 (1.89)	29.9 (9)	86.7	3.2
							Propranolol 80 mg qd	5.83 (1.98)	31.7 (8)	76.7	3.2
Keskinbora 2008 ³⁹	75	DB, COM, RCT	Turkey	18-60 yrs w/Dx of migraine with or without aura defined by IHS within 1 year of study start date, and migraine frequency of 3-12 (max 15) with pain intensity > 5 over 3 months preceding study	Use of ergots or triptans and/or another prophylactic within 4 weeks of study start date, severe depression, other type HA, allergy to topiramate and/or amitriptyline, and hepatic, renal, or heart disease	12	Topiramate 25-200 mg qd	6.3 (3.25)	32.3 (9.39)	70	16.7
							Amitriptyline 10-150 mg qd	6.09 (2.56)	37.9 (8.67)	63.6	21.4
							Topiramate 25-200 + amitriptyline 10-150 mg qd	6.05 (2.75)	39.1 (9.13)	66.7	8.7
Krymchantowski 2002 ⁴⁰	39	DB, COM	Brazil	Dx with transformed HA from overusing symptomatic medications	N/A	9	Amitriptyline 20 mg bid	27.4	36.4 (2.5)	63.2	32
							Amitriptyline 20 mg + fluoxetine 20 mg bid	24.2		70	30
Diener 2002 ⁴¹	808	MC, DB, COM (EQ)	Germany, Spain, Switzerland, Italy, Belgium	18-65 yrs w/Dx of migraine with or without aura defined by IHS within 1 yr of study date and a migraine frequency of 2 to 6 migraines per month over the 2 months preceding the study; interval HA permitted only if occurrence < 6/month	Any prophylactic use 2 months preceding study, depression, extrapyramidal disorders, asthma, COPD, bronchospasms, heart failure, AV block, hypotension, peripheral vascular disease, diabetes, hepatic, renal cardiovascular, malignant, or respiratory disease, alcohol/drug dependence, pregnancy, lactation, childbearing potential without birth control, no pain-free interval of 24 hours between migraine attacks, poor compliance during run-in period	16	Flunarizine 5 mg qd	3.1 (2.3-3.9)	37 (18-66)	79.1	16.7
							Flunarizine 10 mg qd (5 days of the week)	3.0 (2.1-3.8)	37 (18-63)	81.8	19.3
							Propranolol 160 mg qd	3.0 (2.9-3.2)	37 (17-65)	83.3	16.7
Rao 2000 ⁴²	259	DB, COM	India	Patients attending an outpatient department of neurology and neurosurgery and had 2 or more attacks per week	N/A	12	Cyproheptadine 2 mg bid	N/A	28.6 (16-53)	67.2	23.6
							Propranolol 40 mg bid				17.7
							Cyproheptadine 2 mg + propranolol 40 mg bid				11.6
							Placebo				30.4

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TABLE 2 Persistence Data from Randomized Controlled Trials of Oral Migraine Prophylaxis (continued)

Reference	N	Design	Study Country	Inclusion Criteria	Exclusion Criteria	Study Length (Weeks)	Treatment	Baseline Headache Frequency Mean (SD)	Age Mean (SD) or Median (Range)	% Female	Discontinuation Rates (%)
Kaniecki 1997 ⁴³	37	SB, PC, CO, RCT	USA	18-60 yrs w/Dx of migraine with or without aura defined by IHS within 1 year of study start date, and migraine frequency of 3-12 (max 15) with pain intensity >5 over 3 months preceding study.	Past trial of divalproex or propranolol, failure of 2 trials of migraine prophylactic, severe medical or psychiatric illness, analgesic use >15 days per month, alcohol/drug abuse, lack of contraception use by potential childbearing women	12	Propranolol 60 mg tid	4.38 (2.8)	N/A	81.8	3
							Divalproex 500 mg tid				11
							Placebo				0
Bank 1994 ⁴⁴	64	DB, COM, RCT	Hungary	Patients w/Dx of migraine defined by IHS	N/A	12	Fluvoxamine 50 mg qd	N/A	34.5 (7.4)	71.9	15.6
							Amitriptyline 25 mg qd				31.3
Pradalier 1989 ⁴⁵	74	MC, DB, PC, RCT	France	18-65 yrs w/Dx of migraine with or without aura defined by IHS for at least 2 yrs preceding the study and had 2-8 crises per month	No prior prophylactic treatment during 2 weeks preceding the study, congestive heart failure, heart block, bradycardia (<50 beats/min), Raynaud's, high blood pressure, resistance to 2 previous trials of migraine prophylactics, no other concomitant medication (only usual acute migraine medications allowed)	16	Propranolol LA 160 mg qd	1.66 (0.23) per week	37.1 (1.7)	77.5	45.0
							Placebo	1.40 (0.20) per week	37.7 (1.8)	73.5	44.1
Mikkelsen 1986 ⁴⁶	39	DB, PC, CO, RCT	Sweden	18-65 yrs w/Dx of common or classic migraine defined by the 1962 Ad Hoc Committee on Classification of Headache for at least 1 yr preceding the study and at least 3 attacks per month	Allergy to study medication; serious heart, kidney, liver, or psychiatric conditions; asthma, bronchitis, diabetes, active ulceration, pregnancy or breast feeding; concomitant migraine prophylactic within 1 month of study start date	12	Propranolol 40 mg tid	N/A	38 (15-65)	N/A	7.7
							Tolfenamic acid 100 mg tid				7.7
							Placebo				5.1
Ryan 1984 ⁴⁷	48	DB, COM, RCT	USA	21-65 yrs w/primary Dx of common or classic migraine, at least 3 migraine attacks per month	Pregnancy or not taking birth control if of potential childbearing age, hypersensitivity to beta blockers, significant GI disorder, cluster HA, CHF, sinus bradycardia, severe mitral or aortic valve disease, COPD, CAD, asthma, diabetes, recent MI, hepatic or renal impairment, hyperthyroidism, any psychosis or central nervous system disease, or intracranial disease	12	Nadolol 80 mg qd	6.13	N/A	72.9	6.3
							Nadolol 160 mg qd	5.56			0
							Propranolol 160 mg qd	7.42			12.5
Tfelt-Hansen 1984 ⁴⁸	96	MC, DB, PC, CO, RCT	Denmark, Norway, Finland	18-65 yrs w/ 2-6 common migraine attacks per month as defined by the 1962 Ad Hoc Committee on Classification of Headache	Any other type of HA, head injury, contraindications to beta blockers, fertile women not using birth control, women on oral contraceptives, heart rate <54 beats/min and/or diastolic blood pressure ≤100 mmHg	12	Timolol 10 mg bid	5.97 (3.39)	39.5 (9.9)	N/A	19.7
							Propranolol 80 mg bid				15.6
							Placebo				13.5
Andersson 1981 ⁴⁹	49	DB, COM, CO	Denmark	22-68 yrs w/at least 3 attacks per month in the preceding 2 months defined as paroxysmal HA associated with discomfort, possibly inability to work, and 1 or more of the following: nausea, vomiting, visual disturbances, and paresthesia	Previous treatment w/ propranolol, contraindication to beta blocker, treatment with neuroleptic drugs, thymoleptic drugs, or minor tranquilizers, serious liver or kidney diseases	12	Propranolol 80 mg bid	N/A	38	69.4	10.2
							Femoxetine 200 mg bid				14.3

AV=atrioventricular; avg=average; bid=twice daily; CAD=coronary artery disease; CD=claims database; CHF=congestive heart failure; CM=chronic migraine; CO=crossover; COM=comparative; COPD=chronic obstructive pulmonary disease; DB=double blind; Dx=diagnosis; EQ=equivalence; FD=fixed dose; GI=gastrointestinal; HA=headache; ICHD=International Classification of Headache Disorders; IHS=International Headache Society; MAOI=monoamine oxidase inhibitor; MC=multicenter; MEMS=medication event monitoring system; MI=myocardial infarction; mo=months; mmHG=millimeter of mercury; MPR=medication possession ratio; N/A=not available; NI=noninterventive; OL=open label; PC=placebo controlled; PD=pooled data; PI=phone interview; PRO=prospective; qd=once daily; RCT=randomized controlled trial; RET=retrospective; SA=single arm; SB=single blind; SSRI=selective serotonin re-uptake inhibitor; SUR=survey; tid=3 times daily; yrs=years.

TABLE 3 Pooled Discontinuation Rates from Randomized Controlled Trials

	Study Length	
	8-12 Weeks	16-26 Weeks
Topiramate		
Total number of patients	125	1,331
Number of patients who discontinued	15	573
Discontinuation rate	12.0%	43.1%
Persistence (1–discontinuation rate)	88.0%	56.9%
Amitriptyline		
Total number of patients	79	381
Number of patients who discontinued	24	172
Discontinuation rate	30.4%	45.1%
Persistence (1–discontinuation rate)	69.6%	54.9%
Propranolol		
Total number of patients	355	453
Number of patients who discontinued	49	104
Discontinuation rate	13.8%	23.0%
Persistence (1–discontinuation rate)	86.2%	77.0%
Placebo		
Total number of patients	241	676
Number of patients who discontinued	36	275
Discontinuation rate	14.9%	40.7%
Persistence (1–discontinuation rate)	85.1%	59.3%

summarized as part of the systematic review. Discontinuation data from RCTs were pooled, weighted by sample size, and stratified by drug and length of study. Average persistence rates (1–discontinuation) and reasons for discontinuation cited in RCTs were examined for each medication.

Results

Search Results

Searches returned a total of 1,254 articles, of which 788 were found to be unique. Abstracts were reviewed for 96 studies that met the inclusion/exclusion criteria, of which 48 were subsequently excluded because of incomplete or missing discontinuation data. The absence of data was, in part, caused by a number of crossover studies, especially among propranolol RCTs, that did not report discontinuation rates in the study results. A further 4 studies were available only in Spanish ($n = 1$), Portuguese ($n = 1$), or German ($n = 2$); 6 reported data on patients included in other studies (open-label extension studies or post hoc analyses); 2 examined relapse after discontinuing the study medication; and 3 were expert opinion. Included studies ($N = 33$) are shown in Table 1, which lists observational studies that examined adherence and persistence, and Table 2, which lists the RCTs of the 3 prophylactic medications and the rate of discontinuation reported in each study.

Observational Studies: Adherence

Of the 6 observational studies that examined migraine prophylaxis adherence, 1 used electronic MEMS to assess adherence,¹² while 3 reported outcomes based on self-report,^{16–18} and 2 used retrospective claims analysis to calculate MPR.^{19,20} Five of the 6 studies were conducted in the United States, with time horizons ranging from 4 to 56 weeks. The sixth study was conducted in Germany and used a time horizon of 80 weeks. All studies used a wide variety of medications from the 3 major therapeutic classes of oral migraine prophylaxis agents—anticonvulsants, antidepressants, and antihypertensives—except for 1, which restricted the study medications to anticonvulsants.¹⁸ Medication dosage was not considered in any of the studies. Across studies, adherence ranged from 41% to 95% at 2 months and declined over time to 21% to 80% at 6 months and 35% to 56% at 12 months. Individual study data are shown in Table 1.

Observational Studies: Persistence

Four open-label studies were identified that evaluated topiramate^{21–23} or amitriptyline alone,²⁴ while 2 comparative studies evaluated divalproex and topiramate,²⁵ and flunarizine and propranolol.²⁶ Studies were conducted in Germany,^{21–23} Austria,²⁴ Belgium,²⁶ the Netherlands,²⁷ and Brazil.²⁵ Dosages varied by individual patient but were within the range of approved FDA-labeled dose for migraine prophylaxis, where applicable. Persistence was also evaluated in 2 large claims database analyses that included a wide range of medications from the 3 major classes of oral migraine prophylaxis, without regard for dose.^{27,28} These studies report that persistence ranged from 41% to 88% at 2 months, 19% to 79% at 6 months, and 7% to 55% at 12 months. Individual study data are shown in Table 1.

Randomized Controlled Trials: Persistence

Since persistence can be calculated as the inverse of discontinuation, persistence can be inferred from discontinuation rates reported in RCTs. Nineteen RCTs provided sufficient data on discontinuation, as part of trial design, among propranolol, amitriptyline, and topiramate. The populations of migraine patients were generally similar, as evidenced by the similar age and gender distributions and comparable recruitment criteria (inclusion/exclusion) across the RCTs reviewed. Differences were assumed to be negligible; therefore, results were pooled and weighted by sample size to calculate a weighted average discontinuation rate for each medication of interest (Table 3). Although some studies evaluated medications other than those included in this review, only patients on propranolol, amitriptyline, topiramate, and placebo were pooled. Time horizons varied across studies, ranging from 8 weeks to 26

FIGURE 2 Combined Weighted Persistence Rates from Randomized Controlled Trials

weeks. This difference was adjusted for by stratifying into 2 separate groups: 8-12 weeks and 16-26 weeks. The weighted average discontinuation rate of each medication and placebo were compared for each time horizon group and presented in Figure 2 as the proportion of patients who stayed persistent (calculated as 1–discontinuation at the end of the study time horizon). The primary reasons for discontinuation across the different medications were also compared and summarized in Table 4 as well as Figure 3. The pooled data show that persistence declines rapidly over time, with nearly half of RCT participants discontinuing from clinical trials of amitriptyline and topiramate by 12-26 weeks (45% and 43%, respectively). Adverse events were the most common reason for discontinuation cited, especially among patients treated with topiramate (24%) and amitriptyline (17%). Individual study data from each RCT are available in Table 2.

Discussion

This review demonstrated a downward trend in migraine prophylaxis adherence and persistence over time that is similar to that seen for other chronic disease states. Adherence and persistence were shown to be below the acceptable threshold (<80%) after 6 months among both observational and RCT data. While study heterogeneity limits the ability to compare across all available data, this review of the literature has produced several important findings. First, there was a substantially lower rate of discontinuation among RCTs evaluating propranolol compared with amitriptyline or topiramate. The reason for this low rate of discontinuation among patients taking propranolol is unknown. However, the propranolol RCTs

TABLE 4 Discontinuation Rates by Cause

	Topiramate (%)	Amitriptyline (%)	Propranolol (%)	Placebo (%)
Adverse events	23.70	16.74	7.77	6.96
Patient choice	5.56	18.56	1.21	6.25
Lost to follow-up	3.43	6.30	2.95	3.77
Other	8.45	9.53	6.97	15.45

were generally conducted earlier (1980s) than the other 2 medications reviewed, which may have influenced RCT design, data capture, or documentation of study discontinuation. In addition, the types of RCTs for propranolol are largely small studies, potentially reducing the discontinuation rate if trial participants were more closely managed.

Aside from differences in study duration, RCTs were not adjusted for differences in study design, and this absence of adjustment may bias the results if there were systematic differences in the rate of discontinuation in amitriptyline, propranolol, and topiramate RCTs that are unrelated to the study drug. Counterintuitively, pooled discontinuation rates for the placebo groups across all studies had similar rates of discontinuation compared with amitriptyline and topiramate. However, when stratified by primary reported reason for discontinuation, placebo differs from active agents in the drivers of discontinuation. Placebo has very low rates of discontinuation because of adverse events and very high discontinuation for other reasons (including lack of therapeutic effect), while discontinuation of active interventions was mostly attributed to adverse events.

FIGURE 3 Weighted Discontinuation Rate by Cause

Limitations

This review is subject to several important limitations. There are many oral agents used for migraine prophylaxis. For this systematic review, only the 3 most common oral medications were reviewed. However, the 3 medications described here are each a member of the 3 major therapeutic classes of oral agents used as migraine prophylaxis (anticonvulsants, antidepressants, and beta blockers) and thus may be somewhat representative of the therapeutic class as a whole. Another important note is that pooling results across studies may not be appropriate, given differences in study design, geographic region population, dosing, etc. For this reason, we refrained from combining the results of observational studies. The discontinuation rates and reason for study withdrawal from RCTs may not be generalizable to the real-world patient experience of these agents because of the structured program of care employed in clinical trials. We acknowledge that such bias exists, but that it is likely to produce a conservative estimate of persistence rates, as those enrolled in a clinical trial are potentially less likely to discontinue taking the drug. Furthermore, in 3 of the 14 observational studies, adherence was calculated using patient-reported data. While this methodology allows for convenient real-world data collection, it has been shown to overestimate adherence rates.^{29,30} Conversely, using MPR may underestimate adherence because some patients may have withdrawn from therapy because such therapy is no longer indicated. Migraine frequency and severity fluctuate over time in many patients, and some patients may discontinue prophylaxis because it is no longer warranted. Given the data available, we were unable to assess the ongoing clinical need for

prophylaxis and thus may underestimate persistence if a large proportion of patients withdraw from therapy because it is no longer indicated. Despite these limitations, we believe that this study helps provide a broad overview of adherence and persistence to oral migraine prophylaxis and highlight the need for future studies to investigate this topic.

Conclusion

Observational studies as well as pooled data from RCTs support that oral migraine prophylactics have poor adherence and persistence. New options with improved tolerability and/or fewer dosing intervals may improve patient adherence to oral migraine prophylaxis treatments. Adherence should be considered as an endpoint in future studies exploring the use of such therapies.

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DISCLOSURES

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Hepp participated in planning the study, collecting the data, conducting the analysis, and interpreting the results. Bloudek participated in planning the study and interpreting the results. Varon participated in planning the study, collecting the data, conducting the analyses, and interpreting the results. Hepp and Bloudek wrote the first draft. All authors critically reviewed and edited the first draft and subsequent revisions of the manuscript. All authors approved the final manuscript before submission.

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