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Research Submission

Triptans in the Acute Treatment of Migraine: A Systematic Review and Network Meta-Analysis

Chris Cameron, *MSc; Shannon Kelly, *BSc; Shu-Ching Hsieh, PhD; Meghan Murphy, MSc; Li Chen, MSc; Ahmed Kotb, MSc; Joan Peterson, BA; Doug Coyle, PhD; Becky Skidmore, MLS; Tara Gomes, MHSc; Tammy Clifford, PhD; George Wells, PhD

Background.—Although triptans are widely used in the acute management of migraine, there is uncertainty around the comparative efficacy of triptans among each other and vs non-triptan migraine treatments. We conducted systematic reviews and network meta-analyses to compare the relative efficacy of triptans (alone or in combination with other drugs) for acute treatment of migraines compared with other triptan agents, non-steroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid (ASA), acetaminophen, ergots, opioids, or anti-emetics.

Methods.—The Cochrane Library, MEDLINE, and EMBASE were searched for randomized controlled trials that compared triptans (alone or in combination with other drugs) with placebo-controlled or active migraine treatments. Study selection, data extraction, and quality assessment were completed independently by multiple reviewers. Outcome data were combined and analyzed using a Bayesian network meta-analysis. For each outcome, odds ratios, relative risks, and absolute probability of response were calculated.

Results.—A total of 133 randomized controlled trials met the inclusion criteria. Standard dose triptans relieved headaches within 2 hours in 42 to 76% of patients, and 2-hour sustained freedom from pain was achieved for 18 to 50% of patients. Standard dose triptans provided sustained headache relief at 24 hours in 29 to 50% of patients, and sustained freedom from pain in 18 to 33% of patients. Use of rescue medications ranged from 20 to 34%. For 2-hour headache relief, standard dose triptan achieved better outcomes (42 to 76% response) than ergots (38%); equal or better outcomes than NSAIDs, ASA, and acetaminophen (46 to 52%); and equal or slightly worse outcomes than combination therapy (62 to 80%). Among individual triptans, sumatriptan subcutaneous injection, rizatriptan ODT, zolmitriptan ODT, and eletriptan tablets were associated with the most favorable outcomes.

From the School of Epidemiology, Public Health and Preventive Medicine, University of Ottawa, Ottawa, Canada (C. Cameron, D. Coyle, T. Clifford, and G. Wells); University of Ottawa Heart Institute, Ottawa, Canada (C. Cameron, S. Kelly, S. Hsieh, M. Murphy, L. Chen, A. Kotb, J. Peterson, B. Skidmore, and G. Wells); Keenan Research Centre of the Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Canada (T. Gomes); CADTH, Ottawa, Canada (T. Clifford).

Address all correspondence to G. Wells, School of Epidemiology, Public Health and Preventative Medicine, University of Ottawa, Ottawa, Ontario K1Y 4W7, Canada, email: gawells@ottawaheart.ca

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*Co-first authors.

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Interpretation/Conclusions.—Triptans are effective for migraine relief. Standard dose triptans are associated with better outcomes than ergots, and most triptans are associated with equal or better outcomes compared with NSAIDs, ASA, and acetaminophen. Use of triptans in combination with ASA or acetaminophen, or using alternative modes of administration such as injectables, may be associated with slightly better outcomes than standard dose triptan tablets.

Key words: triptan, efficacy, benefit, migraine, systematic review, network meta-analysis

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Migraine is a common and potentially disabling neurological condition characterized by recurrent moderate to severe pain generally occurring on one side of the head. Globally, it is estimated that over 10 to 15 percent of people suffer from migraines.[1] The condition causes short- and long-term disability, reduces quality of life, and often impacts work productivity, social relationships, and family life.[2-4]

The acute management of migraines includes the use of non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, ergots, opioids, and triptans. For many patients with moderate to severe migraine, triptans are considered the first-line therapy. There are now seven triptans (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan) available in Canada. The relative efficacy of each triptan among each other is uncertain since the majority of triptan studies have been placebo controlled. Further, while other reviews[3-10] have attempted to examine the relative efficacy of triptans among each other and vs non-triptan migraine treatments, these studies have not considered multiple routes of administration (tablets, oral disintegrating tablets, injection, nasal spray, rectal suppositories), combination triptan therapy, or dose.

Therefore, as part of a larger initiative by the Ontario Drug Policy Research Network to evaluate triptans for the acute treatment of migraine in adults and provide recommendations for funding changes of these drugs in Ontario (http://odprn.ca/drug-class-review/completed-reviews/triptans/), we conducted a systematic review and network meta-analysis to address the following research question: What is the evidence for the efficacy, effectiveness, and safety of triptans (alone or in combination with other drugs) for acute treatment of migraines compared with: other triptan agents, NSAIDs, acetylsalicylic acid (ASA), acetaminophen, ergots, opioids, or anti-emetics?

METHODS

Data Sources and Searches.—Published randomized controlled trials (RCTs) were identified using electronic search strategies developed and tested by an experienced medical information specialist in consultation with the review team. Using the OVID platform, we searched Ovid MEDLINE®, Ovid MEDLINE® In-Process & Other Non-Indexed Citations, and Embase Classic + Embase to identify English-language RCTs published from inception to October 6, 2013. Using the Cochrane Library on Wiley, the Cochrane Database of Systematic Reviews and CENTRAL were also searched. Strategies utilized a combination of controlled vocabulary (eg, migraine disorders, tryptamines) and keywords (eg, triptans, rizatriptan, sumatriptan). Vocabulary and syntax were adjusted across databases. Additional references were also sought through hand searching the bibliographies of relevant articles. Gray literature was searched using Google Scholar and the clinical trial sites listed in CADTH's Grey Matters (http://cadth.ca/resources/grey-matters). Complete details of the electronic search strategy, including any limits used, are reported in Appendix S1.

Study Selection.—The protocol was peer reviewed and published online prior to the start of the review. Studies were eligible for inclusion in the systematic review if they satisfied the population, intervention, comparator, and outcome (PICO) statement, including the study designs of interest outlined in our protocol.

The population of interest were adults 18 years and older with migraine specified by the International Headache Society (IHS 1988; IHS 2004, IHS ICDH-2).

Studies which included patients with cluster, tension or other headaches, chronic or recurrent migraines who are not experiencing an acute episode were not included. Active and placebo-controlled RCTs were selected for inclusion if they were published in English and included at least one triptan under review. The following triptans were included in the review: almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan. Triptans were allowed to be used alone or in combination with other drugs. All routes of administration (tablets, oral disintegrating tablets, injection, nasal spray, and rectal suppositories) and all doses (any frequency or strength) were included. Doses are classified according to Table 1. Allowable comparator groups include: placebo; other triptans used either alone or in combination with other acute migraine therapies; or other acute pharmacologic migraine treatment options (eg, NSAIDs, ASA, acetaminophen, ergots, opioids, antiemetics). Numerous outcomes were considered and results are reported elsewhere: http://odprn.ca/drug-class-review/completed-reviews/triptans/; however, the focus of this publication are: headache relief at 2 hours; freedom from pain at 2 hours; sustained headache response at 24 hours; sustained freedom from pain at 24 hours; and use of rescue medication. In general, headache relief was defined as a reduction in headache intensity from moderate or severe to mild or none at 2 or 24 hours, whereas freedom from pain was defined as the percentage of patients pain-free at 2 and 24 hours.

Screening, Data Extraction, and Quality Assessment.—In the first phase of screening, the titles and abstracts of all identified citations were screened by two independent reviewers (MM, JP). In the second phase of screening, full manuscripts were retrieved and screened by two independent reviewers on the basis of our predefined patient population, intervention, comparison, outcomes, and study design of interest. We only included RCTs/crossovers that reported data for the first attack. Disagreements were resolved through discussion or through adjudication by a third reviewer (SK). For each included study, one of four reviewers independently (MM, JP, SCH, AK) extracted the data on characteristics of trial participants, study characteristics, and details on each study arm/pharmacological intervention, including but not limited to: dose, frequency, route of administration, co-medication/prophylaxis, and results of the clinical safety and efficacy outcomes for the overall study population and the *a priori* subgroups identified. All extracted data were checked for accuracy by another reviewer. Any disagreements in the assessment of these data were resolved through discussion until consensus was reached.

Quality assessment of RCTs was performed independently by four reviewers (MM, JP, SCH, AK) using a standardized table based on major items from the Cochrane Risk of Bias Tool.[11] The trial selection process is presented in a flowchart based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[12,13] statement (Fig. 1).

Table 1.—Dose Categorization for a Migraine Attack (and Number of RCTs/Number of Patients for 2-Hour Relief)†

	Low dose (Half)	Standard dose (Common)	High dose (Double)
Eletriptan	20 mg (3 RCTs/514 patients)	40 mg (13 RCTs/3143 patients)	80 mg (10 RCTs/2042 patients)
Sumatriptan	25 mg (4 RCTs/850 patients)	50 mg (23 RCTs/5870 patients)	100 mg (23 RCTs/5210 patients)
Rizatriptan	5 mg (3 RCTs/752 patients)	10 mg (11 RCTs/2676 patients)	20 mg (1 RCT/82 patients)
Frovatriptan	–	2.5 mg (5 RCTs/1840 patients)	5 mg (2 RCTs/338 patients)
Almotriptan	6.25 mg (2 RCTs/527 patients)	12.5 mg (7 RCTs/2120 patients)	25 mg (2 RCTs/352 patients)
Zolmitriptan	1.25 mg (1 RCT/52 patients)	2.5 mg (10 RCTs/3491 patients)	5 mg (6 RCTs/2084 patients)
Naratriptan	–	2.5 mg (3 RCTs/512 patients)	5 mg (No data)

†Numbers for other outcomes are reported in Appendix S6.
– = no low dose available/relevant for this medication.

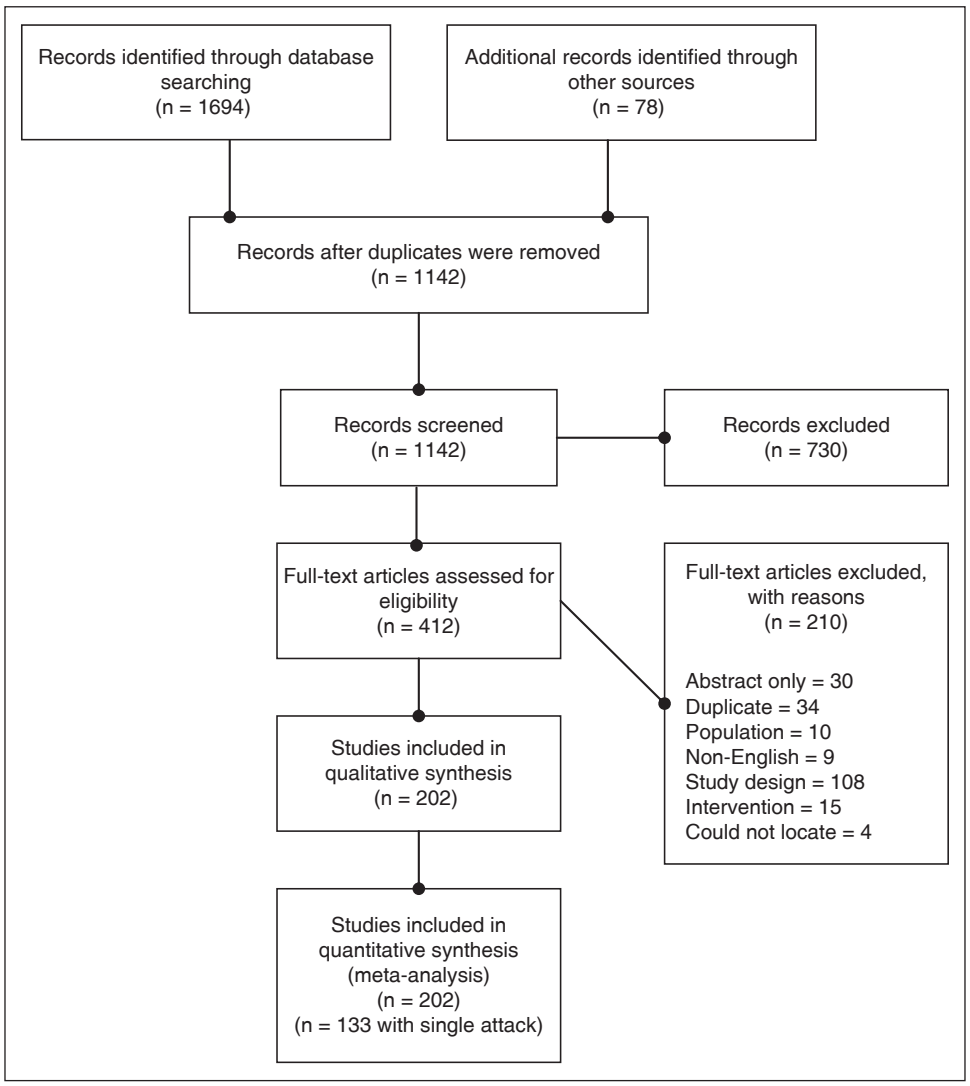

Fig 1.—PRISMA diagram.

Data Synthesis and Analysis.—We performed a Bayesian network meta-analysis. A Bayesian network meta-analysis requires two main elements: a likelihood function derived from a model that specifies the relation between the unknown parameters and the observed data, and prior distributions for the unknown parameters.[14] A prior distribution of a parameter represents the uncertainty of parameter before the data are examined.[14,15] The prior chosen may be informative or "vague" where the latter is thought to let the data drive the analysis. Multiplying the prior and the likelihood function leads to the posterior distribution of the parameter, which is used to carry out all inferences in a Bayesian analysis.[14,15] Methods for Bayesian network meta-analyses allow analysis of both placebo and active comparison studies simultaneously.[14] Both direct and indirect pieces of evidence are combined. The results from indirect evidence combined with the direct evidence may strengthen the assessment between treatments evaluated using Bayesian network meta-analysis. Bayesian network meta-analyses were conducted using WinBUGS software version 1.4.3 (MRC Biostatistics Unit, Cambridge, UK). A binomial likelihood model which accounts for the use of multi-arm trials was used for the analyses given the datasets provided

were dichotomous outcomes and included multi-arm trials.[14] Bayesian network meta-analyses were conducted for the following outcomes: headache relief within 2 hours; freedom from pain at 2 hours; sustained headache response at 24 hours; sustained freedom from pain at 24 hours; and use of rescue medication. Placebo was chosen as the reference group or index node in the model. Both random-effects network meta-analyses using informative priors and fixed-effects analyses were conducted;[14,15] assessment of model fit and choice of model was based on assessment of the deviance information criterion (DIC) between study standard deviation and comparison of residual deviance to number of unconstrained data points.[16,17]

Point estimates and 95% credible intervals for odds ratios (OR) were derived using Markov Chain Monte Carlo methods for all nodes in analysis. Risk ratios and absolute risk for an outcome of interest were estimated based on the ORs and the mean proportion of patients who experience the outcome in the placebo arms among included studies. Vague priors, such as $N(0, 100^2)$, were assigned for basic parameters throughout[17] and informative priors for the variance parameter based on evidence on the extent of heterogeneity observed in previous meta-analyses, as described in Turner et al.[15] To ensure convergence was reached, trace plots and the Brooks–Gelman–Rubin statistic were assessed.[15,18] Three chains were fit in WinBUGS for each analysis, with at least 20,000 iterations, and a burn-in of at least 20,000 iterations.[18,19]

We also qualitatively compared the results from our network meta-analysis with direct pairwise estimates. We formally assessed inconsistency by comparing the deviance between study variance and DIC statistics in fitted consistency and inconsistency models.[20] We also plotted the posterior mean deviance of the individual data points in the inconsistency model against their posterior mean deviance in the consistency model to identify any loops where inconsistency is present.[20] We also conducted a sensitivity analysis adjusting for control group response rate to address heterogeneity among included studies and generated a box plot to illustrate differences among included studies.

RESULTS

Search Results.—The initial literature search returned 1694 database abstracts and 78 gray literature documents (Fig. 1). After duplicates were removed, 1142 remained to be assessed for inclusion and 730 were excluded. Of the 412 full-text articles reviewed, 202 full-text publications were included after applying the PICO criteria. Of these, 69 were excluded from analysis as they did not present single migraine attack data. A total of 133 publications reported single migraine attack data in 133 unique RCTs. A complete list of included and excluded studies is available in Appendix S2.

Characteristics of Included Studies.—A detailed list of included studies, patients and study characteristics is provided in the technical report. All included studies were published between 1991 and 2012. Most were large, multicenter studies conducted in a variety of countries worldwide, and often across many different countries. The number of randomized patients was often bigger than the number of participants included in the effect estimates for outcomes in each trial, due to the fact that most trials reported modified intention to treat outcome populations, ie, based on recruited patients who subsequently experienced a migraine event. The trials all recruited migraine sufferers who met the International Classification of Headache Disorders (ICHD) for migraine headaches,[21-24] or used inclusion criteria with sufficient comparability to the ICHD criteria. All studies generally included patients affected with migraine with or without aura, and a small number also included some patients with menstrual migraine.[25-27] Four RCTs reported solely on menstrual migraine in female participants.[28-31] All participants self-administered their study medications. Trial participants were generally between the ages of 18 and 65, with an average age of approximately 40. Very few trials included participants older than 65, and trials of children and adolescents were excluded by the PICO statement. Trial participants were predominantly female. In 133 studies reporting first attack data, the mean percent of females included was over 80%. Patients included in studies were both treatment naïve and experienced. In general, a high proportion of studies included participants with at least one

previous treatment failure with a triptan. The risk of bias assessment for each study is available upon request.

Headache Relief at 2 Hours.—The evidence network for headache relief at 2 hours included 96 studies and a total of 56,180 participants (Table 2). Overall, 45 different treatments were considered, providing for 287 comparisons. There is some evidence of inconsistency in the network (Appendix S3). Standard dose (SD) triptans relieved headaches within 2 hours in 42 to 76% of patients, compared with 27% for placebo. Sumatriptan subcutaneous injection (76%), rizatriptan ODT (69%), zolmitriptan ODT (66%) had the largest effect on 2-hour headache relief among monotherapies, whereas ergots (38%), frovatriptan (42%), naratriptan (46%), and ASA (46%) were associated with less favorable outcomes. SD triptans yielded equal or slightly worse outcomes than triptan combination therapies (62% to 80%). Detailed results are reported in Table 3 including credible intervals around point estimates.

Freedom From Pain at 2 Hours.—The evidence network for freedom from pain at 2 hours included 88 studies and a total of 50,929 participants. Overall, 41 different treatments were considered, involving 236 comparisons. There was no evidence of inconsistency in the network (Appendix S3). With SD triptans, only 18 to 50% of patients had freedom from pain within 2 hours, compared with 11% for placebo. Rizatriptan ODT (50%), eletriptan tablet (39%), rizatriptan tablet (37%), sumatriptan subcutaneous injection (37%), and zolmitriptan ODT (37%) had the largest effect on 2-hour freedom from pain among monotherapies, whereas ergots (16%), naratriptan (18%), NSAIDs (22%), and acetaminophen (22%) were associated with less favorable outcomes. SD triptans yielded equal or slightly worse outcomes than triptan combination therapies (37% to 51%). Detailed results are reported in Table 3 including credible intervals around point estimates.

Sustained Headache Relief at 24 Hours.—The evidence network for headache relief at 24 hours included 29 studies and a total of 22,963 participants. Overall, 24 different treatments were compared, involving 102 comparisons. There was no evidence of inconsistency in the network (Appendix S3). SD triptans provided sustained headache relief at 24 hours ranging from 29% to 50%, compared with 17% for placebo. Zolmitriptan ODT (50%) and eletriptan tablet (47%) had the largest effect on 24 hour headache relief among monotherapies, whereas ergots (8%), acetaminophen (29%), ASA (29%), and rizatriptan (29%) were associated with less favorable outcomes. SD triptans yielded equal or slightly worse outcomes than triptan combination therapies (46% to 50%). Detailed results are reported in Table 3 including credible intervals around point estimates.

Sustained Freedom From Pain at 24 Hours.—The evidence network for freedom from pain at 24 hours included 42 studies and a total of 27,755 participants. Overall, 20 different treatments were considered, involving 115 comparisons. There was no evidence of inconsistency in the network (Appendix S3). Eighteen to 33% of patients on SD triptans had sustained

Table 2.—Summary of Patient and Study Characteristics for Each Evidence Network:† Headache Relief at 2 Hours, Freedom From Pain at 2 Hours, Sustained Headache Relief at 24 Hours, Sustained Freedom From Pain at 24 Hours, and Use of Rescue Medications

	2-hour headache relief	2-hour freedom from pain	24-hour sustained headache relief	24-hour sustained freedom from pain	Use of rescue medications
Number of studies	96	88	29	42	88
Number of treatment nodes	45	41	24	20	34
Number of participants	56,180	50,929	22,963	27,775	48,363
Number of comparisons	287	236	102	115	222
Number of 2-arm trials	46	47	13	23	50
Number of multi-arm trials	50	41	16	19	38

†Evidence networks consisted of a large number of nodes, which makes it difficult to illustrate graphically.

Table 3.—Percent of Patients (and 95% Credible Interval) Achieving: Headache Relief at 2 Hours, Freedom From Pain at 2 Hours, Sustained Headache Relief at 24 Hours, Sustained Freedom From Pain at 24 Hours, and Use of Rescue Medications†,‡

	2-hour headache relief		2-hour freedom from pain		24-hour sustained headache relief		24-hour sustained freedom from pain		Use of rescue medications	
	% (95%CrI)	OR (95%CrI)	% (95%CrI)	OR (95%CrI)	% (95%CrI)	OR (95%CrI)	% (95%CrI)	OR (95%CrI)	% (95%CrI)	OR (95%CrI)
Placebo	26.70% (25.7%,27.7%)	NA	10.60% (10.0%,11.3%)	NA	17.00% (15.9%,18.2)	NA	9.60% (8.9%,10.3%)	NA	51.60% (50.4%,52.%)	–
TABLET SD										
Almotriptan	48.30% (42.4%,54.2%)	2.56 (2.0,3.3)	24.50% (20.1%,29.6%)	2.73 (2.1,3.6)	35.70% (29.2%,43.0)	2.71 (2.0,3.7)	20.80% (15.9%,26.8%)	2.48 (1.8,3.5)	32.00% (26.1%,38.5%)	0.44 (0.3,0.6)
Eletriptan	60.40% (56.1%,64.6%)	4.19 (3.5,5.0)	39.20% (34.1%,44.7%)	5.43 (4.3,6.9)	47.30% (43.4%,51.3%)	4.37 (3.7,5.3)	32.90% (27.5%,38.7%)	4.63 (3.5,6.1)	21.10% (17.9%,24.7%)	0.25 (0.2,0.3)
Frovatriptan	42.40% (35.6%,49.5%)	2.02 (1.5,2.7)	34.70% (25.4%,45.9%)	4.48 (2.8,7.3)	– –	– –	– –	– –	31.00% (16.5%,50.6%)	0.42 (0.2,1.0)
Naratriptan	44.50% (35.6%,53.8%)	2.2 (1.5,3.2)	17.50% (11.8%,25.0%)	1.79 (1.1,2.8)	38.60% (30.7%,46.8%)	3.06 (2.1,4.3)	18.40% (12.0%,26.8%)	2.13 (1.3,3.5)	30.30% (23.0%,38.8%)	0.41 (0.3,0.6)
Rizatriptan	57.10% (52.4%,61.9%)	3.66 (3.0,4.5)	36.60% (31.7%,42.0%)	4.86 (3.9,6.2)	29.30% (23.7%,35.5%)	2.02 (1.5,2.7)	23.90% (19.0%,29.5%)	2.97 (2.2,4.0)	30.00% (25.6%,34.8%)	0.4 (0.3,0.5)
Sumatriptan	49.70% (46.3%,53.1%)	2.71 (2.4,3.1)	27.70% (24.6%,31.0%)	3.22 (2.7,3.8)	33.10% (30.3%,36.0%)	2.41 (2.1,2.8)	22.80% (2.0%,26.0%)	2.79 (2.3,3.4)	33.80% (30.0%,37.8%)	0.48 (0.4,0.6)
Zolmitriptan	50.00% (45.5%,54.7%)	2.75 (2.3,3.3)	27.10% (22.7%,32.0%)	3.14 (2.5,4.0)	37.60% (33.4%,42.2%)	2.94 (2.4,3.6)	22.50% (18.0%,27.6%)	2.74 (2.0,3.7)	28.00% (22.8%,33.7%)	0.36 (0.3,0.5)
TABLET LD										
Almotriptan tablet	43.30% (33.9%,53.3%)	2.1 (1.4,3.1)	18.50% (11.1%,29.4%)	1.92 (1.0,3.5)	31.70% (24.0%,40.4%)	2.26 (1.5,3.3)	– –	– –	– –	– –
Eletriptan tablet	52.50% (44.3%,60.5%)	3.03 (2.2,4.2)	28.50% (20.8%,37.6%)	3.35 (2.2,5.1)	37.70% (29.8%,46.5%)	2.95 (2.1,4.3)	24.60% (18.3%,32.1%)	3.07 (2.1,4.5)	24.50% (18.7%,31.6%)	0.3 (0.2,0.4)
Frovatriptan tablet	27.30% (18.7%,38.0%)	1.03 (0.6,1.7)	12.60% (5.6%,24.4%)	1.21 (0.5,2.8)	– –	– –	– –	– –	36.70% (20.4%,56.7%)	0.54 (0.2,1.2)
Naratriptan tablet	– –	– –	– –	– –	– –	– –	– –	– –	35.30% (20.7%,53.4%)	0.51 (0.2,1.1)
Rizatriptan tablet	51.20% (43.1%,59.2%)	2.88 (2.1,4.0)	27.50% (18.8%,38.2%)	3.19 (2.0,5.2)	– –	– –	– –	– –	34.30% (24.3%,45.8%)	0.49 (0.3,0.8)
Sumatriptan tablet	44.20% (37.1%,51.7%)	2.17 (1.6,2.9)	24.90% (14.9%,38.0%)	2.79 (1.5,5.2)	29.80% (23.2%,37.1%)	2.07 (1.5,2.9)	– –	– –	46.40% (31.5%,62.0%)	0.81 (0.4,1.5)
Zolmitriptan tablet	44.00% (27.1%,62.2%)	2.16 (1.0,4.5)	21.00% (8.5%,41.7%)	2.24 (0.8,6.1)	29.50% (17.1%,45.6%)	2.04 (1.0,4.1)	– –	– –	33.10% (13.2%,58.8%)	0.46 (0.1,1.4)
TABLET HD										
Almotriptan tablet	50.60% (40.4%,60.8%)	2.81 (1.9,4.3)	32.40% (23.1%,43.2%)	4.04 (2.5,6.4)	– –	– –	– –	– –	28.00% (19.3%,38.6%)	0.36 (0.2,0.6)
Eletriptan tablet	66.20% (61.6%,70.6%)	5.38 (4.4,6.6)	48.00% (41.5%,54.7%)	7.78 (5.9,10.3)	50.50% (45.4%,55.9%)	4.98 (4.0,6.3)	38.90% (32.0%,46.2%)	6 (4.4,8.3)	18.10% (14.5%,22.3%)	0.21 (0.2,0.3)

Table 3.—Continued

	2-hour headache relief		2-hour freedom from pain		24-hour sustained headache relief		24-hour sustained freedom from pain		Use of rescue medications	
	% (95%CrI)	OR (95%CrI)	% (95%CrI)	OR (95%CrI)	% (95%CrI)	OR (95%CrI)	% (95%CrI)	OR (95%CrI)	% (95%CrI)	OR (95%CrI)
Frovatriptan tablet	40.30%	1.85	35.20%	4.58	–	–	–	–	32.30%	0.45
	(30.1%,51.5%)	(1.2,2.9)	(22.5%,50.7%)	(2.4,8.8)	–	–	–	–	(17.3%,51.8%)	(0.2,1.0)
Rizatriptan tablet	64.20%	4.92	50.10%	8.44	–	–	–	–	–	–
	(47.9%,77.8%)	(2.5,9.6)	(32.3%,67.9%)	(4.0,17.9)	–	–	–	–	–	–
Sumatriptan tablet	53.40%	3.14	32.10%	3.99	36.00%	2.75	27.90%	3.65	27.40%	0.35
	(49.8%,56.9%)	(2.7,3.6)	(28.6%,35.8%)	(3.4,4.8)	(32.7%,39.4%)	(2.3,3.2)	(23.8%,32.4%)	(2.9,4.6)	(24.2%,30.8%)	(0.3,0.4)
Zolmitriptan tablet	51.40%	2.9	31.00%	3.79	38.30%	3.02	23.90%	2.97	33.40%	0.47
	(45.4%,57.5%)	(2.3,3.7)	(24.8%,38.3%)	(2.8,5.3)	(32.7%,44.3%)	(2.4,3.9)	(17.8%,31.8%)	(2.0,4.5)	(23.9%,44.6%)	(0.3,0.8)
ODT SD										
Rizatriptan	69.00%	6.1	50.20%	8.49	–	–	–	–	19.90%	0.23
	(59.6%,77.0%)	(4.1,9.2)	(34.5%,66.7%)	(4.4,17.0)	–	–	–	–	(6.2%,46.0%)	(0.1,0.8)
Zolmitriptan	65.80%	5.28	36.60%	4.87	–	–	–	–	–	–
	(50.6%,78.3%)	(2.8,9.9)	(20.6%,56.8%)	(2.2,11.1)	–	–	–	–	–	–
ODT LD										
Rizatriptan	57.40%	3.7	37.80%	5.11	–	–	–	–	–	–
	(44.6%,69.3%)	(2.2,6.2)	(23.2%,55.5%)	(2.6,10.6)	–	–	–	–	–	–
ODT HD										
Zolmitriptan	–	–	–	–	50.00%	4.88	–	–	24.40%	0.3
	–	–	–	–	(38.0%,62.6%)	(3.0,8.2)	–	–	(16.0%,35.1%)	(0.2,0.5)
NASAL SPRAY SD										
Sumatriptan	52.60%	3.04	21.20%	2.26	–	–	–	–	–	–
	(43.6%,61.5%)	(2.1,4.4)	(6.4%,53.4%)	(0.6,9.8)	–	–	–	–	–	–
Zolmitriptan	51.30%	2.89	–	–	–	–	–	–	–	–
	(38.8%,63.9%)	(1.7,4.9)	–	–	–	–	–	–	–	–
NASAL SPRAY LD										
Sumatriptan	41.80%	1.97	–	–	–	–	–	–	–	–
	(32.6%,51.5%)	(1.3,2.9)	–	–	–	–	–	–	–	–
Zolmitriptan	48.20%	2.55	–	–	–	–	–	–	–	–
	(35.6%,61.0%)	(1.5,4.3)	–	–	–	–	–	–	–	–
NASAL SPRAY HD										
Zolmitriptan	62.30%	4.53	33.80%	4.3	41.40%	3.44	27.30%	3.54	22.00%	0.27
	(54.4%,69.7%)	(3.3,6.3)	(24.5%,44.7%)	(2.7,6.8)	(34.6%,48.5%)	(2.6,4.6)	(20.5%,35.5%)	(2.5,5.2)	(14.9%,31.4%)	(0.2,0.4)
SUBCUTANEOUS INJECTION SD										
Sumatriptan	75.70%	8.54	36.60%	4.87	–	–	23.50%	2.9	23.40%	40.29
	(67.6%,82.5%)	(5.7,12.9)	(25.1%,50.0%)	(2.8,8.5)	–	–	(15.8%,33.6%)	(1.8,4.8)	(17.7%,30.1%)	(0.2,0.4)
Zolmitriptan	–	–	–	–	–	–	–	–	35.00%	0.51
	–	–	–	–	–	–	–	–	(9.1%,74.1%)	(0.1,2.7)

SUBCUTANEOUS INJECTION HD										
Sumatriptan	70.10%	6.45	29.10%	3.46	–	–	–	–	25.50%	0.32
	(46.0%,87.2%)	(2.3,18.7)	(11.9%,57.0%)	(1.1,11.3)	–	–	–	–	(10.1%,50.2%)	(0.1,1.0
PATCH SD										
Sumatriptan	48.30%	2.56	20.60%	2.19	–	–	–	–	26.20%	0.33
	(37.0%,60.0%)	(1.6,4.1)	(12.9%,31.4%)	(1.2,3.9)	–	–	–	–	(12.9%,45.6%)	(0.1,0.8)
SUPPOSITORIES LD										
Sumatriptan	70.80%	6.64	44.70%	6.8	–	–	–	–	–	–
	(49.4%,86.1%)	(2.7,17.0)	(22.4%,71.1%)	(2.4,20.8)	–	–	–	–	–	–
NON TRIPTAN SINGLE THERAPIES										
NSAID	48.00%	2.53	21.80%	2.35	29.10%	2	16.40%	1.85	36.90%	0.55
	(42.3%,53.9%)	(2.0,3.2)	(17.6%,26.8%)	(1.8,3.1)	(25.1%,33.5%)	(1.6,2.5)	(12.6%,20.9%)	(1.4,2.5)	(31.0%,43.1%)	(0.4,0.7)
Acetaminophen	51.70%	2.94	22.20%	2.41	29.30%	2.02	14.30%	1.58	–	–
	(30.8%,72.3%)	(1.2,7.2)	(9.2%,43.7%)	(0.9,6.6)	(16.0%,47.5%)	(0.9,4.5)	(5.0%,32.5%)	(0.5,4.6)	–	–
Aspirin	46.10%	2.35	24%	2.66	–	–	–	–	33.40%	0.47
	(32.1%,60.7%)	(1.3,4.2)	(13.7%,38.4%)	(1.3,5.3)	–	–	–	–	(20.2%,50.1%)	(0.2,0.9)
Ergots	38.40%	1.71	15.50%	1.55	7.90%	0.42	–	–	24.00%	0.3
	(29.5%,47.9%)	(1.2,2.5)	(8.2%,27.1%)	(0.8,3.2)	(1.5%,28.2%)	(0.1,1.9)	–	–	(15.8%,34.9%)	(0.2,0.5)
COMBINATION THERAPIES										
Aspirin with anti-emetic	50.90%	2.85	19.30%	2.01	–	–	–	–	31.70%	0.44
	(41.9%,60.0%)	(2.0,4.1)	(13.0%,27.5%)	(1.3,3.2)	–	–	–	–	(23.0%,41.9%)	(0.3,0.7)
Triptan with acetaminophen	79.90%	10.9	50.50%	8.61	50.30%	4.93	29.30%	3.92	–	–
	(59.6%,92.7%)	(4.1,35.0)	(29.4%,72.3%)	(3.5,22.1)	(32.1%,69.0%)	(2.3,11.0)	(14.1%,50.8%)	(1.5,9.9)	–	–
Triptan with NSAID	62.30%	4.53	36.80%	4.91	46.20%	4.2	32.50%	4.55	22.30%	0.27
	(55.3%,68.9%)	(3.4,6.1)	(31.7%,42.1%)	(3.9,6.2)	(41.3%,51.4%)	(3.4,5.2)	(28.3%,37.0%)	(3.7,5.6)	(18.5%,26.7%)	(0.2,0.3)
OTHER THERAPIES										
SD BI 44370 TA tablet	57.50%	3.71	25.30%	2.86	47.20%	4.36	28.90%	3.83	26.70%	0.34
	(39.3%,73.7%)	(1.8,7.7)	(12.0%,45.2%)	(1.2,7.0)	(31.4%,62.6%)	(2.2,8.3)	(14.4%,49.0%)	(1.6,9.1)	(17.0%,39.3%)	(0.2,0.6)
HD BI 44370 TA tablet	63.40%	4.76	32.40%	4.04	54.30%	5.8	30.30%	4.1	20.90%	0.25
	(45.8%,78.2%)	(2.3,9.8)	(17.1%,52.8%)	(1.7,9.5)	(38.8%,69.2%)	(3.0,11.2)	(15.5%,50.6%)	(1.7,9.7)	(12.9%,32.0%)	(0.1,0.4)
LD BI 44370 TA tablet	38.20%	1.7	9.20%	0.85	20.30%	1.24	7.00%	0.7	48.60%	0.89
	(22.1%,57.1%)	(0.8,3.7)	(2.8%,23.4%)	(0.2,2.6)	(9.9%,35.4%)	(0.5,2.7)	(1.4%,20.1%)	(0.1,2.4)	(34.8%,62.8%)	(0.5,1.6)
SD Tonaberstat	30.20%	1.19	5.90%	0.53	–	–	–	–	–	–
	(18.9%,44.6%)	(0.6,2.2)	(2.0%,14.4%)	(0.2,1.4)	–	–	–	–	–	–
LD Tonaberstat	28.00%	1.07	7.00%	0.64	–	–	–	–	–	–
	(17.9%,42.2%)	(0.6,2.0)	(2.6%,16.3%)	(0.2,1.7)	–	–	–	–	–	–
Acetaminophen, dichloralphenazone, and isometheptene	37.70%	1.66	–	–	–	–	–	–	–	–
	(19.1%,60.9%)	(0.7,4.3)	–	–	–	–	–	–	–	–

NA = not applicable; ODT = oral disintegrating tablet; SD = standard dose.

†Percent of patients with the outcome are based on the odds ratios from the network meta-analysis and mean proportion of patients who experience the outcome in the placebo group.

‡Evidence networks include all treatments in this table although results did not change substantially when low dose or experimental agents were excluded.

– = no low dose available/relevant for this medication.

freedom from pain at 24 hours, compared with 10% for placebo. Eletriptan tablet (33%) and rizatriptan tablet (24%) had the largest effect on 24-hour freedom from pain among monotherapies, whereas acetaminophen (14%), ASA (16%), and naratriptan (18%) were associated with less favorable outcomes. SD triptans yielded equal or slightly worse outcomes than triptan combination therapies (29% to 33%). Detailed results are reported in Table 3 including credible intervals around point estimates.

Use of Rescue Medications.—The evidence network for the use of rescue medication included 88 studies and a total of 48,363 participants. Overall, 34 different treatments were considered, providing for 222 comparisons. There was evidence of inconsistency in the network (Appendix S3). With SD triptans, the percent of patients using rescue medications ranged from 20 to 34%, compared with 52% for placebo. The NNT in order for one patient to avoid use of rescue medication ranged from 4 to 6 patients. Eletriptan tablet (21%) and zolmitriptan tablet (24%) required the use of the least amount of rescue medications among monotherapies, whereas NSAIDs (37%), sumatriptan tablet (34%), and ASA (33%) used the most. SD triptans yielded equal or slightly worse outcomes than triptan combination therapies (22%). Detailed results are reported in Table 3 including credible intervals around point estimates.

Comparisons Among the SD Triptans.—Figure 2 provides comparisons among the SD triptan tablets. The gray circle indicates that the triptan identified in the "row" is associated with better outcomes than the "column" triptan; the black circle indicates that the "row" triptan is associated with worse outcome than the "column" triptan; the blank circle indicates that there is no difference between the "row" and "column" triptan; and a missing circle indicates that the outcome was not available for analysis. In general, there were more favorable results observed for eletriptan and rizatriptan (as indicated by the gray circles in the lower portion of the diagonal in Fig. 2). Results were less favorable for naratriptan and frovatriptan. Use of rescue medications was not significantly different between the triptans except for sumatriptan having a significantly favorable result compared with zolmitriptan. Detailed results are reported in Appendix S4.

Sensitivity Analyses.—Figure 3 presents a box plot illustrating control group response rates among treatments included in the network. From Figure 3, it can be seen that some treatments have lower or higher control group response rates than other treatments. We also report findings from a meta-regression analysis adjusting for these differences in control group response rate. Overall, findings for most treatments remained unchanged although those with lower

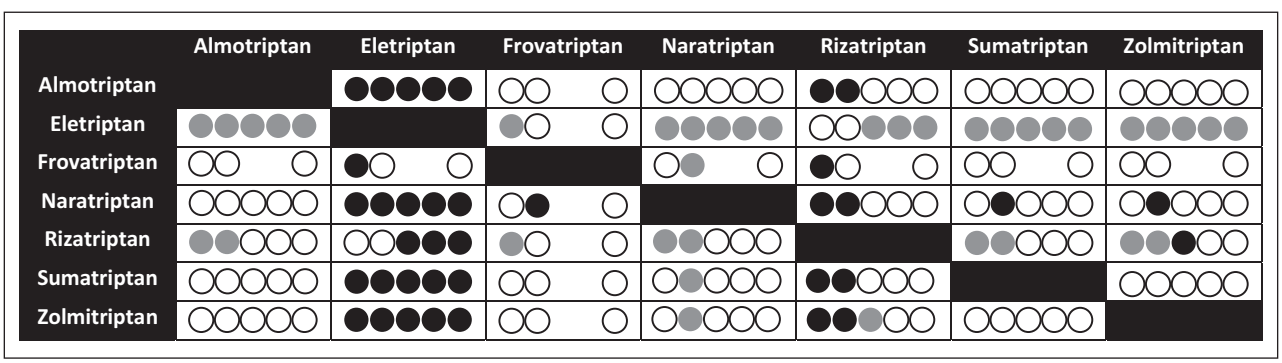

Fig 2.—Comparison among the standard dose triptan tablets on the 5 efficacy outcomes: headache relief at 2 hours, freedom from pain at 2 hours, sustained headache relief at 24 hours, sustained freedom from pain at 24 hours, and use of rescue medications.* *The 5 contiguous circles correspond, respectively, to the 5 efficacy outcomes: headache relief at 2 hours, freedom from pain at 2 hours, sustained headache relief at 24 hours, sustained freedom from pain at 24 hours, and use of rescue medications. The gray circle indicates that the "row" triptan is associated with better outcomes compared with "column" triptan; the black circle indicates that the "row" triptan is worse than the "column" triptan; the blank circle indicates that there is no difference between the "row" and "column" triptan; and a missing circle indicates that the outcome was not available for analysis.

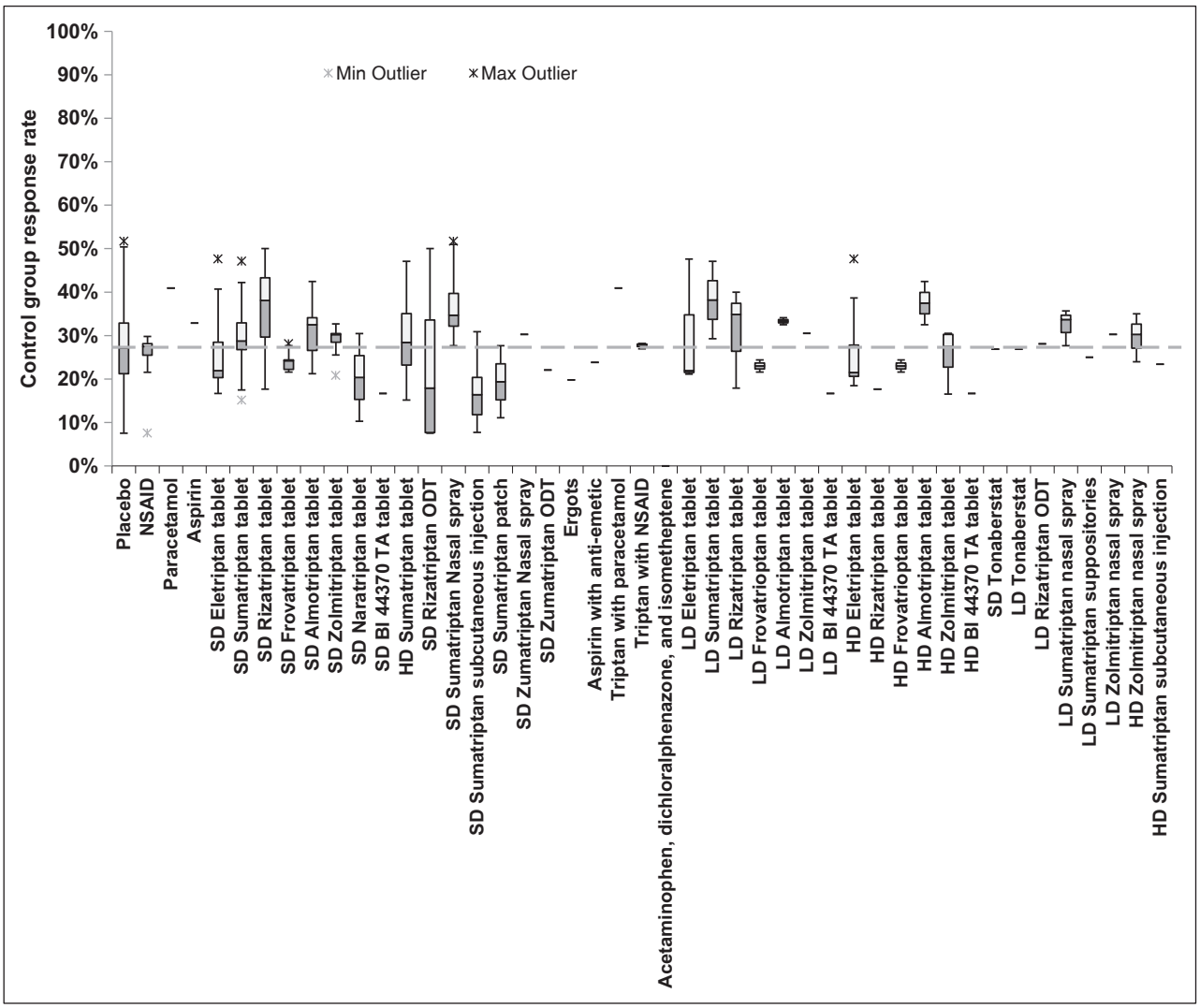

Fig 3.—Comparison of control group response rate among studies for 2-hour response.

control group response rates (eg, SD eletriptan tablet) became slightly less favorable, albeit still more favorable than SD triptan tablets (Appendix S5).

DISCUSSION

We found that SD triptans relieved headaches within 2 hours in 43 to 76% of patients. Freedom from pain within 2 hours was less common, with about 18 to 50% of patients experiencing freedom from pain within 2 hours. SD triptans provided sustained headache relief at 24 hours in 29 to 50% of patients, and sustained freedom from pain at 24 hours in 18 to 33% of patients. Use of rescue medications among patients using SD triptans ranged from 20 to 34%. Our findings align with those reported in other systematic reviews,[3-10] although the majority of other reviews only report estimates of relative effect for SD triptans.

SD triptans were associated with more favorable results than ergots for 2- and 24-hour outcomes, and equal or more favorable results than NSAIDs, ASA, and acetaminophen for 2-hour outcomes. These findings align with recommendations from the Canadian Headache Society Guidelines[3] where they gave a strong recommendation for triptans, NSAIDs, ASA, and acetaminophen but did not recommend ergots for routine use in the acute management of migraine. Similarly, the National Institute for Health and Care

Excellence (NICE) in the UK does not recommend ergots for the acute treatment of migraine, but recommends oral triptans, NSAIDs, ASA, and acetaminophen for the acute treatment of migraine in patients who prefer monotherapy.[32]

We found that combination therapies such as triptan and ASA or triptan plus acetaminophen, and certain modes of administration such as rizatriptan ODT and sumatriptan subcutaneous injection, were associated with slightly more favorable 2-hour results compared with SD triptans. However, there is potential that these findings may be due to systematic differences in the patient population and/or study design; that is, studies assessing efficacy of combination therapies or certain modes of administration may have been more extensively studied in a patient population that is systematically different, ie, more severe and/or treatment experienced. We attempted to adjust for this possible issue by conducting a meta-regression analysis adjusting for placebo response rate, a proxy that is often helpful in identifying patient populations or study designs that are systematically different (Fig. 3). We found that findings for combination therapies such as triptan and ASA or triptan plus acetaminophen remained stable after adjustment, whereas those using other modes of administration became slightly less favorable, albeit still more favorable than SD triptan tablets. Recent NICE guidance recommends combination therapy with an oral triptan and ASA or oral triptan plus acetaminophen, and findings from both our primary analysis and sensitivity analysis seem to support NICE recommendations.[4]

Among individual triptans, our analysis suggests that the majority of triptans, except frovatriptan and naratriptan, deliver similar pain relief in the acute management of migraines. However, our findings also suggest that eletriptan and rizatriptan may provide better pain relief than some of the other triptans. This latter finding should be interpreted in light of a number of caveats. First, findings for eletriptan became slightly less favorable after we adjusted for control groups response rate, albeit still more favorable than other triptans. Second, both eletriptan and rizatriptan are only available in tablet forms, whereas other triptans such as sumatriptan are available in multiple formulations – which can be advantageous for patients given mixing of triptans is ill advised. Finally, we do not consider costs or cost-effectiveness in this paper. Other triptans such as sumatriptan are available as less expensive generics, whereas eletriptan is not yet available as a generic. Our companion pharmacoeconomic report has shown that use of less costly generic triptans could significantly reduce total expenditure on triptans.[32] However, providing more open access to triptans will lead to a significant increase in their use with a high budget impact. NICE in the UK recommends to start with the triptan with the lowest acquisition cost initially, and if this is consistently ineffective, try one or more expensive alternative triptans.[4] Consumer Reports recommends a similar approach, recommending sumatriptan initially because it is available as an inexpensive generic and offers the widest choice for mode of delivery.[2,33]

Studies were not sufficiently powered or of adequate duration to measure differences in long-term complications or adverse events. Future research is needed in assessing the long-term use of triptans in the acute management of recurrent migraines.

As with all analyses, there are several limitations that warrant consideration. First, graphical aids in the form of network diagrams and forest plots are typically provided for network meta-analyses. However, our analysis consisted of upwards 45-treatment nodes when the network was stratified by dose, mode of administration, and combination therapies. The inclusion of evidence structures with a large number of nodes (>20) makes presentation of network diagrams unwieldy. Similarly, presentation of forest plots or tables with all comparisons becomes challenging given the number of treatments and potential comparisons. As such, we provide tables which concisely report the main findings from them in tabular form compared with placebo (Table 3). We also report absolute probability of each comparison.

CONCLUSIONS

Triptans were found to be efficacious for the treatment of acute migraine. Forty-three to 76% of

patients experience pain relief at 2 hours when using SD triptan tablets. Most triptans were associated with equal or more favorable results than NSAIDs, ASA, acetaminophen, and more favorable results than ergots. Use of triptans in combination with aspirin or acetaminophen, or using different modes of administration such as injection, was associated with slightly better results than SD triptan tablets.

STATEMENT OF AUTHORSHIP

Category 1

(a) Conception and Design
Chris Cameron; Shannon Kelly; George Wells; Tara Gomes

(b) Acquisition of Data
Shu-Ching Hsieh; Meghan Murphy; Ahmed Kotb; Joan Peterson; Becky Skidmore

(c) Analysis and Interpretation of Data
Chris Cameron; Li Chen; Shannon Kelly; George Wells; Doug Coyle; Tammy Clifford; Tara Gomes

Category 2

(a) Drafting the Manuscript
Chris Cameron; Shannon Kelly

(b) Revising It for Intellectual Content
George Wells; Tara Gomes; Doug Coyle; Shu-Ching Hsieh; Meghan Murphy, Joan Peterson; Becky Skidmore; Ahmed Kotb; Tammy Clifford; Li Chen

Category 3

(a) Final Approval of the Completed Manuscript
Chris Cameron; Shannon Kelly; George Wells; Tara Gomes; Doug Coyle; Tammy Clifford; Shu-Ching Hsieh; Meghan Murphy; Joan Peterson; Becky Skidmore; Ahmed Kotb; Li Chen

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Appendix S1.—Search strategy.
Appendix S2.—Included studies.
Appendix S3.—Assessment of inconsistency.
Appendix S4.—Comparisons among standard dose triptans.
Appendix S5.—Adjustment for control group response rate.
Appendix S6.—Number of patients and studies for each outcome.