



REVIEW

Evaluation of Patients with Insufficient Efficacy and/or Tolerability to Triptans for the Acute Treatment of Migraine: A Systematic Literature Review

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ABSTRACT

Introduction: Use of triptans for acute treatment of migraine is associated with insufficient efficacy and/or tolerability in approximately 30–40% of people. We conducted a systematic literature review (SLR) to synthesize definitions, terminology, subsequent treatment outcomes, and characteristics associated with this subpopulation.

Methods: A comprehensive SLR was conducted to identify studies, published from Jan 1995 to

May 2019, which focused on insufficient efficacy and/or tolerability to triptans.

Results: Thirty-five publications were identified, of which 22 described randomized controlled trials and open-label studies, and 13 described observational studies. Across studies, multiple objectives and a high amount of variability in methodologies and outcomes were noted. The most commonly applied measures of efficacy were headache pain freedom and pain relief at 2 h. Ten studies assessed efficacy of switching or optimizing treatment in patients with historical insufficient efficacy or tolerability to previous triptan treatment and demonstrated varying levels of success. Factors associated with increased risk of triptan insufficient efficacy included severe baseline headache severity, photophobia, phonophobia, nausea, and depression.

Conclusions: Irrespective of the methodology or definition used to identify people with insufficient efficacy and/or tolerability to triptans, study results support the assertion that a high unmet need remains for effective acute treatment of migraine.

Keywords: Acute treatment; Insufficient efficacy and/or tolerability to triptans; Migraine; Triptans; Triptan non-responders; Triptan response

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Key Summary Points

This systematic literature review identified substantial variability across studies in definitions and methodologies used to identify insufficient efficacy and/or tolerability to triptans for acute treatment of migraine.

Across studies, the most commonly used outcomes to measure efficacy were pain relief and pain freedom at 2 h.

The totality of evidence suggests that a proportion of patients with insufficient efficacy and/or tolerability to one triptan may benefit from switching to a different triptan.

Factors associated with increased risk of insufficient efficacy and/or tolerability to triptans include severe baseline headache severity, photophobia, phonophobia, nausea, and depression.

Findings from this review suggest that a large unmet need remains for people with insufficient efficacy and/or tolerability to triptans, irrespective of the definitions or methodologies used to identify this population.

DIGITAL FEATURES

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INTRODUCTION

Since their introduction in the 1990s, triptans have been considered therapy of choice for the acute treatment of moderate to severe migraine attacks [1]. Triptans act primarily on 5-HT_{1B}/5-HT_{1D} receptors which are present in multiple

regions including cerebral blood vessels, sensory trigeminal nerves, and trigeminal nucleus caudalis neurons [2]. Activation of these receptors leads to inhibition of release of pro-inflammatory neuropeptides and vasoconstriction [3]. Triptans have been available to patients in the USA for more than 20 years; estimates from a longitudinal US study that evaluated utilization and reimbursement trends point to an increase in triptan prescriptions from 87,348 in 1993 to 1.2 million in 2013 [4]. Globally, triptan use is more challenging to study, in part because of limited data availability, and partly because triptans are available over-the-counter (OTC) in some countries such as the UK, Germany, New Zealand, and Sweden [5–7].

It is estimated that approximately 30–40% of people with migraine are not successfully treated using a triptan, for reasons of insufficient efficacy and/or tolerability [8–10]. Factors including route of administration and time from onset of migraine attack to administration have been shown to influence patients' response to triptans [11, 12]. While methods to assess response vary across studies, it is generally acknowledged that insufficient efficacy and/or tolerability to one triptan does not necessarily predict outcomes with a different triptan. The true population of patients with insufficient efficacy and/or tolerability to triptans is challenging to characterize given the complexity and high level of variability reported across patients, attacks (even within the same person), and treatments [8, 12]. In addition, definitions applied to identify people with triptan insufficient efficacy and/or tolerability vary substantially among studies.

Given the need to better understand this population of patients with migraine and insufficient efficacy and/or tolerability to triptans, we conducted a systematic literature review (SLR) to identify randomized controlled trials (RCTs), open-label studies, and observational studies that focused on evaluating any aspect of this population. Our objectives were to investigate outcomes associated with switching or optimizing acute treatments; to determine definitions and terminologies used to identify and describe this population; and to investigate patient, disease, attack, and treatment

characteristics associated with this population. Robust reviews, meta-analyses, and expert clinical perspectives relevant to this topic have been previously published [8, 9, 12–14]. However, to our knowledge this is the first SLR with a broad scope specific to this population. This information is increasingly relevant as new classes of acute treatments will become options for patients who have insufficient efficacy, tolerability, or contraindications to triptans.

METHODS

Data Sources and Searches

We searched the literature for all relevant RCTs and observational studies of patients with migraine who have been treated with triptans. Using the OVID platform, we searched the following databases: EMBASE, Ovid MEDLINE® and Epub Ahead of Print, In-Process and Other Non-Indexed Citations, Daily and Versions®, EBM Reviews (Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effect), PsychINFO, and EconLit. Search strategies are included in Supplementary Material.

The search strategies utilized a combination of free text searching and subject headings. Vocabulary and syntax were adjusted across databases. We also searched for any additional references by hand-searching bibliographies of relevant articles. Grey literature was carefully explored for any relevant publications since 2017 to present, utilizing clinical trial registries (ClinicalTrials.gov and WHO Internal Clinical Trials Registry Platform) and conference proceedings (Migraine Trust International Symposium [MTIS], Congress of the International Headache Society [IHC], American Headache Society [AHS] Annual Scientific Meeting, European Headache Federation [EHF] Congress, and American Academy of Neurology [AAN] Annual Meeting).

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Study Selection

Studies were included on the basis of Population, Intervention, Comparator, Outcome, Study design (PICOS) criteria for inclusion and exclusion. Studies published from Jan 1995 to May 2019 which included interventions with triptans versus any comparators and focused on insufficient efficacy and/or tolerability to triptans were screened.

Screening Process and Data Extraction

The systematic review process followed guidelines from the Cochrane Handbook of Systematic Reviews of Interventions (CHSRI) [15]. A researcher (DJ) executed the search strategies in each database and exported the results for abstract screening. In the first phase of screening, two independent analysts (NH and JS) reviewed the titles and abstracts of all retrieved publications. Following this, the same two analysts independently examined full-text publications. Any discrepancies were resolved through discussion or through the involvement of a senior reviewer.

Data extraction from eligible studies, utilizing the data extraction form, was performed by one analyst and checked by another analyst against the source publication. Any disagreements in the assessment of these data were resolved by a senior reviewer.

Bias Assessment and Quality Control

Two analysts independently performed quality assessments of RCTs and observational studies. RCTs were assessed for risk of bias using the CHSRI tool [15]. Non-randomized studies were assessed for bias using the Newcastle–Ottawa Scale (NOS) [16].

Following this step, two independent analysts assessed the quality of RCT publications using the National Institute of Health and Care Excellence (NICE) checklist [17]; for observational studies, the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist was used [18]. This study was conducted in accordance with the Preferred

Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) 2009 guidelines [19]. The PRISMA checklist is provided in the Supplemental Material.

Definitions for Pain Freedom and Pain Relief

When referencing efficacy response throughout this review, “pain freedom” refers to complete elimination of pain at endpoint. Unless otherwise stated, “pain relief” generally refers to a decrease in headache pain severity from moderate or severe at baseline to mild or none at endpoint using a 4-point headache severity scale.

RESULTS

Overall Search Results

The initial literature search yielded 4663 abstracts and 382 sources of grey literature. Following screening of abstracts, 45 full-text publications were reviewed, of which 31 publications met PICOS criteria for inclusion (Supplemental Material, Supplementary Table S1) in the qualitative synthesis. Four grey literature records were included in the qualitative synthesis, resulting in a total of 35 publications (Fig. 1). Risk of bias and quality control assessments were performed on 18 RCTs and seven observational studies; results are summarized in Supplemental Material. Overall, 16 RCT publications were judged to have a low or unclear risk of bias, while two had serious risk. Observational studies were judged to have mild or moderate risk of bias, except for one which was judged to have serious risk. The quality control assessments demonstrated that the source population was well described in 14 publications, inclusion/exclusion criteria were clearly detailed in 16 publications, interventions and comparators were adequately described in all studies except one, and relevant outcomes were assessed in all publications.

In several of the studies identified in this review, the definition for prior insufficiency to

triptans was not specific either to only efficacy or only tolerability; the definitions generally could have applied to either or both. Therefore, we used the terminology of insufficient “efficacy and/or tolerability” throughout except in those cases where the definition was clearly attributed to one or the other.

Study Characteristics and Objectives

Of the 35 publications that met criteria for the current analysis, 16 comprised results from randomized, double-blind, placebo-controlled trials; six from open-label studies; and 13 publications disclosed results from observational studies. High-level study overviews with study designs, patient populations, interventions, and outcomes specific to the scope of this review are summarized in Tables 1 and 2. Broader and more detailed descriptions and outcomes of the studies are provided in Supplemental Material (Supplementary Tables S2 and S3). Definitions and terminology used to identify and describe insufficient efficacy and/or tolerability to triptan across the studies are described in Table 3 for RCTs and open-label studies, and in Table 4 for observational studies. Brief summaries of important study characteristics identified within this SLR, with an emphasis on intervention studies are provided.

Terminology and Definitions

The most commonly applied terms to describe people with triptan insufficient efficacy and/or tolerability involved variations of non-response and variations of insufficient response (Tables 3, 4). Lesser used terms involved dissatisfaction and failure to respond. Most studies relied on patients’ self-reports that were largely subjective and allowed for aspects of both self-defined efficacy and tolerability. In studies with definitions that included specific efficacy parameters, pain freedom at 2 h and pain relief at 2 h were the most commonly applied criteria; some of those further designated sustained efficacy or efficacy in two out of three attacks. A small number of studies applied discontinuation of a

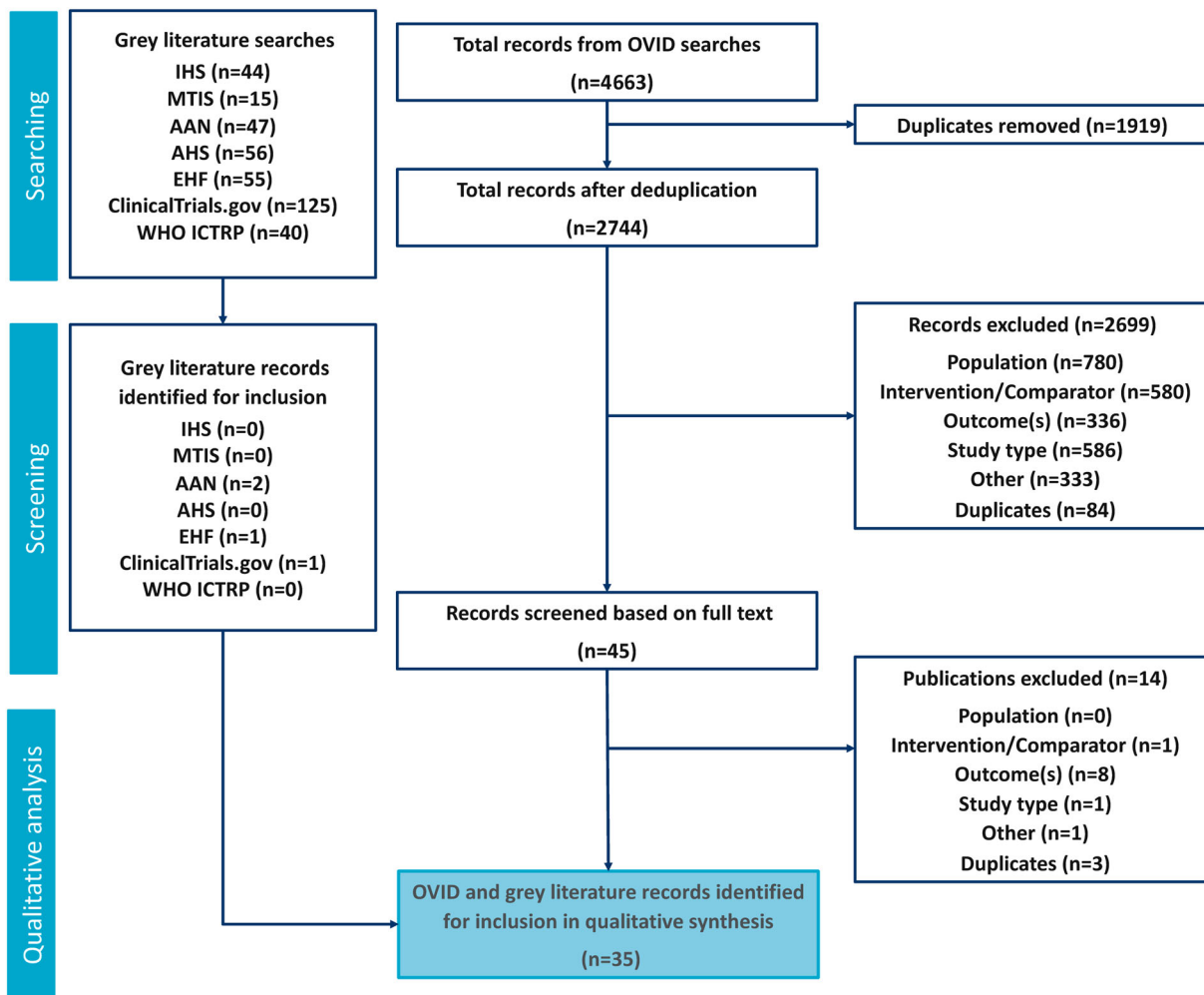


Fig. 1 PRISMA diagram^a. ^aRecords retrieved from the Ovid searches included 2227 abstracts from EMBASE, 1073 from MEDLINE, 911 from EBM reviews, 450 from PyschINFO, and 2 from EconLit. AAN American Academy of Neurology, AHS American Headache Society, EHF European Headache Federation, IHS International

Headache Society, MTIS Migraine Trust International Symposium, WHO ICTRP World Health Organization International Clinical Trials Registry Platform, PICOS Population, Intervention, Comparator, Outcomes, Study design

triptan for reasons of either efficacy or tolerability as criteria.

Switching and Treatment Optimization Study Overview

There were ten switching or treatment optimization studies which were specifically designed to assess efficacy of subsequent acute treatments in patients with historical insufficient efficacy and/or tolerability to triptans

(Table 1). Of these ten studies, seven studied patients with prior sumatriptan [20–26]; one study each studied prior rizatriptan [27], prior treatment with any orally administered triptan [28], and prior treatment with short-acting orally administered triptans [29]. Key efficacy results with subsequent intervention treatments are summarized in Table 1.

Only three of the ten studies screened and validated self-reported prior triptan insufficient efficacy and/or tolerability using an open-label or single-blind run-in phase [20, 21, 23]. In

Table 1 Study characteristics and key results of blinded randomized controlled trials and open-label studies.

Author, year	Study design	Population investigated/key response criteria for inclusion	Intervention investigated	Key results
Patients with historical ^a triptan insufficient efficacy and/or tolerability: subsequent response to different triptan or different triptan dose/formulation (<i>n</i> = 10)				
Seeburger, 2011 [20]	Randomized, blinded, crossover	Previous insufficient efficacy and/or tolerability to sumatriptan ^a Within-trial screening criteria for insufficient efficacy: non-response to sumatriptan 100 mg in one migraine attack eligible to enter double-blind treatment Within-trial screening results: sumatriptan non-responsive: <i>n</i> = 109/159; responsive: <i>n</i> = 44/159	Rizatriptan Rizatriptan 10 mg vs. placebo was assessed over three migraine attacks; 109 patients randomized 1:1:1 to dosing schedule of rizatriptan/rizatriptan/placebo, rizatriptan/placebo/rizatriptan, or placebo/rizatriptan/rizatriptan; 102 participants treated at least one migraine attack, 98 treated all three attacks	Pain relief 2 h (across 3 attacks): rizatriptan: 51%, placebo: 20% Pain-free 2 h (across 3 attacks): rizatriptan: 22%, placebo: 12%. (Number of treated patients 102)
Stark, 2000 [23]	Randomized, blinded, parallel	Previous insufficient efficacy and/or tolerability to sumatriptan ^a Within-trial screening criteria for insufficient efficacy (single-blind assessment): non-responsive to oral administration of sumatriptan 50 mg assessed over one attack Within-trial screening results: sumatriptan non-responsive: <i>n</i> = 220/347; responsive: <i>n</i> = 124/347	Naratriptan Oral administration of naratriptan 2.5 mg (<i>n</i> = 99) vs. placebo (107) assessed over one attack during double-blind period	Pain relief 2 h: naratriptan: 25%; placebo: 10% Pain-free 2 h: naratriptan: 6%; placebo: 3% Pain relief 4 h: naratriptan: 41%; placebo: 19% Pain-free 4 h: naratriptan: 22%; placebo: 10%
Diener, 2005 [21]	Randomized, blinded, parallel	Previous insufficient efficacy and/or tolerability to sumatriptan ^a Within-trial screening criteria for insufficient efficacy: non-response to sumatriptan 50 mg assessed over one attack Within-trial screening results: sumatriptan non-responsive: <i>n</i> = 221/302; responsive: <i>n</i> = 57/302	Almotriptan Almotriptan 12.5 mg (<i>n</i> = 99) vs. placebo (<i>n</i> = 99) assessed over one attack	Pain relief 2 h: almotriptan 12.5 mg: 48%, placebo: 23% Pain-free 2 h: almotriptan: 33%, placebo: 14%

Table 1 continued

Author, year	Study design	Population investigated/key response criteria for inclusion	Intervention investigated	Key results
Farkkila, 2003 [22]	Randomized, blinded, parallel design	Previous insufficient efficacy and/or tolerability to sumatriptan ^a	Eletriptan Eletriptan 40 mg (<i>n</i> = 179), eletriptan 80 mg (<i>n</i> = 167), vs. placebo (<i>n</i> = 81) assessed for treatment of up to 3 attacks	Pain relief 2 h: first attack: eletriptan 40 mg: 59%, eletriptan 80 mg: 70%, placebo: 30% Consistency of response (2/3 attacks): eletriptan 40 mg: 66%; eletriptan 80 mg: 72%; placebo: 15% Consistency of response (all 3 attacks): eletriptan 40 mg: 38%; eletriptan 80 mg: 41%; placebo: 6% Pain-free 2 h: first attack: eletriptan 40 mg: 35%, eletriptan 80 mg: 42%, placebo: 7%
Goldstein, 2006 [27]	Open-label	Previous insufficient efficacy and/or tolerability to rizatriptan ^a	Eletriptan Eletriptan 40 mg (<i>n</i> = 121) assessed for first attack	Pain relief 2 h: eletriptan 40 mg: 64% ^a (95% CI 55–73%) Pain-free 2 h: eletriptan 40 mg: 30% (95% CI 22–39%)
Mathew, 2000 [25]	Open-label, crossover design	Previous insufficient efficacy and/or tolerability to sumatriptan 50 mg ^a	Zomitriptan and rizatriptan Group 1: zolmitriptan 5 mg for first 5 headaches and rizatriptan 10 mg for next 5; Group 2: rizatriptan 10 mg followed by zolmitriptan (<i>n</i> = 48 patients; 120 attacks) to treat 10 attacks in total	Pain relief 2 h (% of attacks): across 10 attacks: zolmitriptan: 73%; rizatriptan: 81% Consistency: 2 out of 3 attacks: zolmitriptan: 81% of attacks; rizatriptan: 80%; 3 out of 3 attacks: zolmitriptan: 72%; rizatriptan: 70% Pain-free 2 h (% of attacks): across 10 attacks: zolmitriptan: 45%; rizatriptan: 58%
Newman, 2008 [26]	Open-label, prospective	Previous insufficient efficacy and/or tolerability to low-dose sumatriptan ^a	Sumatriptan Oral administration of sumatriptan 100 mg (rapid release) early intervention (within 30 min of onset of mild pain); 4 consecutive attacks treated	Pain-free 2 h: range 53–61% across the 4 attacks
Landy, 2004 [24]	Open-label, prospective in headache clinic	Previous insufficient efficacy and/or tolerability to sumatriptan 50 mg ^a	Sumatriptan Sumatriptan 100 mg (<i>n</i> = 20 patients; 60 attacks) at the earliest sign of pain while still mild, in 3 subsequent attacks	Pain-free 2 h (% of attacks): 80% Sustained pain-free 2–24 h: 75%

Table 1 continued

Author, year	Study design	Population investigated/key response criteria for inclusion	Intervention investigated	Key results
Mathew, 2009 [29]	Two identical studies: randomized, double-blind, placebo-controlled, crossover	Previous insufficient efficacy and/or tolerability to a short-acting triptan ^a	Sumatriptan plus naproxen Sumatriptan 85 mg plus naproxen 500 mg vs. placebo (<i>n</i> : study 1: 144; study 2: 139); 2 attacks treated in each trial	Pain-free 2 h (across attacks): Study 1: sumatriptan + naproxen: 40%; placebo: 17% Study 2: sumatriptan + naproxen: 44%; placebo: 14% Sustained pain-free 2–24 h (across attacks): Study 1: sumatriptan + naproxen: 26%; placebo: 8%; Study 2: sumatriptan + naproxen: 31%; placebo: 8%
Diamond, 2007 [28]	Open-label study in headache clinic	Previous insufficient efficacy and/or tolerability to any orally administered triptan ^a	Sumatriptan 6 mg sumatriptan (SC) (<i>n</i> = 43) to treat 3 attacks	Pain relief 2 h : first attack: 91%; second attack: 82%; third attack: 72% Pain-free 2 h : first attack: 56%; second attack: 49%; third attack: 51% Sustained pain free 2–24 h : first attack: 32%; second attack: 32%; third attack: 35%
Patients with historical triptan insufficient efficacy and/or tolerability: subgroup analyses with subsequent non-triptan oral acute treatments (<i>n</i> = 3)				
Blumenfeld, 2019 [32]	Pooled subgroup analysis of two randomized, double-blinded, studies	Previous insufficient efficacy and/or tolerability to any triptan ^a	Ubrogepant Ubrogepant 50 mg/100 mg (study 1) or ubrogepant 25 mg/50 mg (study 2) vs. placebo (1:1:1 ratio) were assessed over a single attack (mITT population: study 1: <i>n</i> = 1327; study 2: <i>n</i> = 1355). Baseline results: 23–27% had triptan insufficient response; 32–42% were triptan-naïve; 35–40% were triptan responders	Pain-free 2 h : response rates were higher for ubrogepant vs. placebo across the triptan subpopulations for treatment of a single attack

Table 1 continued

Author, year	Study design	Population investigated/key response criteria for inclusion	Intervention investigated	Key results
Kniewel, 2018 [33]	Post hoc analysis of two pooled randomized, blinded studies	Prior insufficient efficacy and/or tolerability to any triptan ^a	Lasmiditan Lasmiditan 100, 200 mg vs. placebo assessed in good, poor, or non-responders	Pain-free 2 h: benefit with lasmiditan versus placebo was generally unaffected by prior triptan therapy response. Percentages of patients reporting pain freedom with lasmiditan and placebo were not reported in abstract
Ho, 2011 [31]	Post hoc analysis of one randomized, blinded, parallel design study	Previous insufficient efficacy and/or tolerability to any triptan ^a	Telcagepant and zolmitriptan Telcagepant 150 mg, telcagepant 300 mg, zolmitriptan 5 mg, and placebo (ratio 1:1:1:1) were assessed in patients with good historical triptan response (HTR) (<i>n</i> = 660), intermediate HTR (<i>n</i> = 248), and poor HTR/no use (<i>n</i> = 450)	Pain relief 2 h: Good HTR: zolmitriptan: 72%, telcagepant 300 mg: 52%; telcagepant 150 mg: 48%; placebo: 26%; intermediate HTR: zolmitriptan: 47%, telcagepant 300 mg: 58%; telcagepant: 58%, placebo: 29% Poor HTR/no use: zolmitriptan: 40%, telcagepant 300 mg: 57%; telcagepant 150 mg: 48%, placebo: 31% Pain-free 2 h: Good HTR: zolmitriptan: 44%, telcagepant 300 mg: 23%, telcagepant 150 mg: 18% placebo: 9% Intermediate HTR: zolmitriptan: 29%, telcagepant 300 mg: 34%; telcagepant 150 mg: 23%; placebo: 8% Poor HTR/no use: zolmitriptan: 14%, telcagepant 300 mg: 29%; telcagepant 150 mg: 13%, placebo: 12%

Table 1 continued

Author, year	Study design	Population investigated/key response criteria for inclusion	Intervention investigated	Key results
Subsequent attacks: different or same triptan results ($n = 2$)				
Tietjen, 2005 [34]	Randomized, crossover design	Patients with no response (self-defined meaningful relief/satisfaction) to oral administration of naratriptan 2.5 mg during a migraine attack were screened for enrollment; 35/60 patients had no response	Naratriptan plus prochlorperazine Naratriptan 2.5 mg plus prochlorperazine 25 mg rectal suppository vs. naratriptan 2.5 mg plus placebo were assessed; subjects and investigators blinded to rectal suppository content; of 15 patients who enrolled in the study, 14 completed	Significant decreases in headache severity and disability at 2 h and 4 h were observed with both regimens; however, there were no differences between regimens
Landy, 2014 [66]	Post hoc pooled analysis of 4 randomized, blinded, studies	Insufficient efficacy with eletriptan 40 mg in the first attack (intervention results reported on the basis of patients who did not achieve pain relief at 2 h with eletriptan 40 mg in attack 1)	Eletriptan Eletriptan 40 mg vs. placebo was assessed over 3 attacks. First attack screening results: no pain relief at 2 h: eletriptan 40 mg: 297/1299 patients, placebo 375/1299 patients. Patients with no 2 h pain relief with eletriptan in first attack and who treated all three attacks received eletriptan 40 mg ($n = 170$) or placebo ($n = 193$) in the 2nd and 3rd attacks	Pain relief 2 h: attack 2: eletriptan 49%; placebo 20%; attack 3: eletriptan: 37%; placebo 16% Pain free 2 h: attack 2: eletriptan 17%; placebo 4%; attack 3: eletriptan 19%; placebo 3%
Same attack: second dose with same treatment ($n = 2$)				
Scott, 1996 [64]	Randomized, blinded, parallel design (conducted in general practice centers)	Insufficient efficacy to the first dose of sumatriptan 100 mg (no pain relief at 4 h)	Sumatriptan Sumatriptan 100 mg (second dose) vs. placebo assessed in patients who did not respond to first dose First-dose screening results: lack of pain relief at 4 h with sumatriptan 100 mg in 30% of 1349 patients	Pain relief 4 h: after second dose (range over 3 treated attacks): sumatriptan 100 mg: 51–63%; placebo: 51–61%

Table 1 continued

Author, year	Study design	Population investigated/key response criteria for inclusion	Intervention investigated	Key results
Spierings, 2009 [67]	Randomized, double-blinded	Insufficient efficacy to the first dose of frovatriptan 2.5 mg	Frovatriptan Frovatriptan 2.5 mg for first attack; frovatriptan 2.5 mg vs. placebo for second attack (<i>n</i> = 547 enrolled patients of which 486 treated moderate or severe headache)	In first attack, 63% of 486 patients with moderate or severe headache had no pain relief at 2 h after the first dose. Of 486 patients, 173 (36%) did not take a second dose of study medication at 2 h for non-response (rapid responders). Among rapid responders, 84% and 98% reported mild or no pain at 2 h and 4 h, respectively. Among rapid responders, 24-h recurrence rate was 6% Second attack results not provided
Predictors of insufficient efficacy within a single attack (<i>n</i> = 2)				
Cady, 2007 [35]	Two identical randomized, blinded studies Aim: assessment of patient-reported symptoms of cutaneous sensitivity (SCS) as a negative predictor of response	Patients with migraine with/without aura with history of attacks that were typically mild at onset	Rizatriptan Rizatriptan 10 mg or placebo with early treatment (within 1 h while pain still mild) was assessed over one attack Symptoms of SCS were present pre treatment in 22–29% of patients across the two studies Patient numbers were rizatriptan: <i>n</i> = 353 (study 1) and 331 (study 2); placebo: <i>n</i> = 177 (study 1) and 169 (study 2)	Pain-free 2 h: Baseline symptoms of SCS: rizatriptan 55–58%; placebo 24–35% No baseline symptoms of SCS: rizatriptan 58–59%; placebo 29–33%
Diener, 2008 [45]	Pooled analysis of 10 randomized, blinded, parallel design studies	Patients with migraine with/without aura	Eletriptan Negative predictors of response with eletriptan 20 mg, eletriptan 40 mg, eletriptan 80 mg, or sumatriptan 100 mg vs. placebo were assessed (<i>n</i> = 8473 patients for first-attack data)	Pain free 2 h: eletriptan 20 mg: ~ 15%; eletriptan 40 mg: ~ 30%; eletriptan 80 mg: ~ 35%, sumatriptan 100 mg: ~ 25%; placebo: ~ 5% Multivariate regression analyses identified severe headache pain, presence of photophobia/phonophobia, and presence of nausea as significant baseline predictors of failure to achieve 2-h pain-free response. Time of dosing following headache onset did not show influence

Table 1 continued

Author, year	Study design	Population investigated/key response criteria for inclusion	Intervention investigated	Key results
Repeated attacks insufficient efficacy ($n = 1$)				
Miljkovic, 2018 [70]	Randomized, blinded, parallel design	Patients with migraine without aura	Ergot-based formulation vs. sumatriptan Ergot-based formulation (Nomigren[®]) vs. sumatriptan (dose unspecified) was assessed ($n = 201$ patients)	Pain-free 2 h: Nomigren [®] : 51%; sumatriptan: 34%; Pain-free 2 h: repeat attacks only: Nomigren [®] : 51%, sumatriptan: 24%
Menstrual migraine ($n = 2$)				
Brandes, 2009 [63]	Randomized, blinded, parallel design	Patients with difficult-to-treat menstrual migraine and historical insufficient efficacy and/or tolerability to any triptan ^a	Frovatriptan Frovatriptan 2.5 mg (loading dose: 5 mg) vs. placebo was assessed for short-term prevention of migraine. Two dosing regimens (qd or bid) were studied. A 6-day regimen (starting 2 days prior to anticipated migraine) was used ($n = 410$)	Headache-free peri-menstrual periods (mean number of per patient): frovatriptan qd: 0.69; frovatriptan bid: 0.92; placebo: 0.42 Severity and incidence of difficult-to-treat menstrual migraine were significantly reduced in both frovatriptan arms
Cady, 2014 [65]	Randomized, blinded, parallel design	Patients with menstrual migraine Single menstrual migraine episode	Sumatriptan plus naproxen Sumatriptan 85 mg + naproxen 500 mg (Treximet) ($n = 21$) vs. placebo ($n = 20$) were to be taken at onset of menstrual migraine episode	Migraine recurrence within 24 h post treatment occurred in 2/14 patients treated with Treximet and 0/11 placebo-treated patients Mean time to pain-free was: Treximet: 3.9 h ($n = 14$); placebo: 7.64 h ($n = 10$)

bid twice daily, *h* hour, *qd* once daily

^a Criteria to define historical insufficient efficacy and/or tolerability for each of the 10 studies is described in Table 3 below

those three studies, 21–36% of patients who reported prior insufficient efficacy to sumatriptan experienced pain relief at 2 h with sumatriptan during the trial. Among the patients with confirmed insufficient efficacy and/or tolerability, for the outcome of pain freedom at 2 h, 6% subsequently responded to naratriptan 2.5 mg, 33% to almotriptan 12.5 mg, and 22% to rizatriptan 10 mg ODT (orally disintegrating tablets). For the outcome of pain relief at 2 h, 25% subsequently responded to naratriptan 2.5 mg, 48% to almotriptan 12.5 mg, and 51% to rizatriptan 10 mg (ODT; over three attacks). In all three studies, patients were instructed to

treat the migraine attack when pain was moderate or severe.

Three of the ten studies investigated responses to a different orally administered triptan (monotherapy) without a run-in validation phase. Two were early intervention studies and are discussed in the respective sections [25, 27]. The other, in which patients were instructed to treat while pain was moderate or severe, was conducted in patients who had previously discontinued orally administered sumatriptan [30]. In that study, 35–42% experienced pain freedom at 2 h and 59–70% of patients subsequently treated with eletriptan 40 mg or 80 mg experienced pain relief at 2 h.

Table 2 Study characteristics and key results of observational studies

Author, year	Study design	Patient population; characteristics investigated	Study description or intervention	Results (key relevant findings)
Characteristics investigated in triptan insufficient efficacy and/or tolerability				
Sheftell, 2010 [42]	6-month observational study using data recorded in e-diaries	Patients with migraine who were prescribed any triptan	Any triptan Headache return with any triptan including sumatriptan, rizatriptan, eletriptan, zolmitriptan, almotriptan, sumatriptan injection, triptan nasal spray (<i>n</i> = 359 patients who treated 2168 attacks)	Pain freedom or pain relief at 2 h: 66% of attacks Headache returned by 48 h: 19% of attacks, across 320 patients Factors associated with increased likelihood of headache return: more severe baseline headache, short duration since diagnosis of migraine, female gender
Terrazzino, 2010 [43]	Cohort study	Patients with migraine with/without aura	Any triptan Specific genetic markers predictive of consistency in headache response to any triptan including eletriptan, rizatriptan, almotriptan, frovatriptan, sumatriptan, and zolmitriptan were assessed	Consistent response to triptans was observed in 67% of patients with migraine (87/130); 33% (43/130) of patients did not consistently respond. Consistent responders to each triptan (<i>n</i>): eletriptan: 33; rizatriptan: 29; sumatriptan: 20; frovatriptan: 18; almotriptan: 21; zolmitriptan: 9 Patients who had undergone preventive treatment versus who had not appeared to, responded more consistently to triptan therapy Results support role of STin2 VNTR polymorphism of serotonin transporter gene in conferring higher risk of inconsistent response to triptans

Table 2 continued

Author, year	Study design	Patient population; characteristics investigated	Study description or intervention	Results (key relevant findings)
Munjal, 2016 [36]	Cohort study	Patients with episodic migraine	Any triptan Impact of allodynia on triptan (any) response	Pain-free 2 h: overall: 44% ($n = 3621$) No pain-free 2 h: triptan users with allodynia: 50%; triptan users without allodynia: 36%; non-triptan use with allodynia: 65%; non-triptan use without allodynia: 51% Inadequate response to medication more likely in the presence of allodynia among triptan and non-triptan users
Silberstein, 2019 [37]	Case-control study	Patients with migraine	Any triptan Opioid use, rebound headache, and healthcare resource utilization with any triptan were analyzed using data from electronic medical records, and patient and physician surveys	Triptan insufficient responders were 3 times more likely than responders to suffer from rebound headaches, 3 times more likely to be admitted to a hospital in the past year, 13 times more likely to receive an opioid, and had 37% more visits to a healthcare professional in the past year
Peng, 2016 [40]	Cohort study in headache clinic	Patients with migraine using/recently prescribed sumatriptan	Sumatriptan Patients were asked for effectiveness and AE of sumatriptan 50 mg for their migraine attacks ($n = 1024$ patients); demographics and comorbidity characteristics assessed	Overall effectiveness (definition unspecified) rate of treatment with one tablet sumatriptan 50 mg: 61.3% Responders to sumatriptan, compared to non-responders, were older (mean 40.6 vs. 37.2 years), had milder headache intensity (mean 6.4 vs. 6.7 on 0–10 scale), had lower scores in Beck Depression Inventory (mean 10.6 vs. 12.1), and have regular coffee intake

Table 2 continued

Author, year	Study design	Patient population; characteristics investigated	Study description or intervention	Results (key relevant findings)
Wang, 2017 [44]	Cohort study in headache clinic	Patients with migraine prescribed with sumatriptan	Sumatriptan Sumatriptan 50 mg tablet ($n = 1499$ enrolled patients)	Pain relief 2 h (in at least 2 out of 3) attacks: 69% Regular coffee consumption positively associated with effectiveness of sumatriptan. Compared to non-responders, responders had lower psychiatric measures (Beck Depression Inventory: mean 10.5 vs. 11.8) and lower baseline headache frequency (mean 9.8 vs. 11.6 days per month)
Patrick, 2000 [39]	Long-term (1 year) observational cohort study	Patients with migraine who had participated in zolmitriptan trials	Zolmitriptan Quality of life associated with oral administration of zolmitriptan 5 mg ($n = 1383$)	A significantly greater improvement in MSQOL score was observed in patients who had pain relief at 2 h and pain freedom at 2 h, compared with non-responders Post treatment, responders had MSQOL scores approximately 5 points higher than those of non-responders Non-responders had lower baseline MSQOL scores (by approximately 4 to 7 points) than responders

Table 2 continued

Author, year	Study design	Patient population; characteristics investigated	Study description or intervention	Results (key relevant findings)
Sarchielli, 2006 [38]	Cohort study across 3 headache centers	Triptan-naïve patients with migraine without aura	<p>Rizatriptan</p> <p>Clinical and biochemical correlates associated with rizatriptan responders and non-responders ($n = 20$, 10 each for responders and non-responders). Response was defined as achieving pain relief at 2 h (without 48 h recurrence) to rizatriptan 10 mg in at least 3 consecutive attacks</p>	<p>CGRP and NKA levels measured at baseline were significantly higher in those with baseline sufficient efficacy vs. those with insufficient efficacy</p> <p>1 h after rizatriptan administration, a decrease in CGRP and NKA levels was evident in those with sufficient efficacy, and this corresponded to significant pain relief and alleviation of accompanying symptoms. Those with insufficient efficacy had less significant variations in CGRP and NKA levels at all time points</p> <p>Insufficient efficacy appeared to be correlated with a lesser degree of trigeminal activation, lower variations of trigeminal neuropeptides after triptan administration, and no evidence of parasympathetic activation at baseline</p>

Table 2 continued

Author, year	Study design	Patient population; characteristics investigated	Study description or intervention	Results (key relevant findings)
Seo, 2016 [41]	Observational case-control study in headache clinic	Triptan-naïve patients with migraine	Frovatriptan Patients were instructed to take frovatriptan 2.5 mg as early as possible after migraine attack. Demographic, clinical, and psychiatric variables were investigated (<i>n</i> = 128 patients)	No pain relief 4 h in at least 1 out of 2 consecutive attacks in 22% of patients. In patients with major depressive disorder (MDD), 50% had no pain relief (4 h); MDD was identified as a risk factor Pain relief 4 h in at least 1 out of 2 consecutive attacks in 78% of patients; 92% of responder patients, achieved response in first attack and responded in second attack as well
Specific populations				
al Deeb, 1997 [69]	Prospective cohort study in 2 hospitals	Patients with migraine in Saudi Arabia	Sumatriptan Orally administered sumatriptan 100 mg to be taken as soon as possible and maximally within 2 h after each of two attacks (<i>n</i> = 63 patients). Better response of two attacks reported. Neurologist assessed efficacy on a 4-point scale on the basis pain diminution along a pain severity scale (severe: 3; moderate: 2; mild: 1; none: 0)	3-point drop 4 h : 33% 2-point drop 4 h (better of 2 treated attacks): 33% 1-point drop 4 h (better of 2 treated attacks): 14% No drop 4 h in either attack: 19%
Linder, 1996 [71]	Cohort study	Pediatric patients with migraine	Sumatriptan (SC) Subcutaneously administered sumatriptan 0.06 mg/kg (<i>n</i> = 50 children)	Pain relief reported in 78% of patients; 22% had no or suboptimal response Migraine with episodic tension-type headaches/chronic tension-type headaches was much more frequent in the female patients and, in general, was more difficult to treat

Table 2 continued

Author, year	Study design	Patient population; characteristics investigated	Study description or intervention	Results (key relevant findings)
Switching or discontinuation of triptans				
Sheftell, 2004 [68]	Retrospective cohort study	Patients with migraine with current use of triptans	<p>Any triptan</p> <p>Any triptan including sumatriptan (subcutaneous, nasal, oral), zolmitriptan, rizatriptan, naratriptan and, almotriptan was allowed</p>	<p>Incomplete or no relief as reason for switching a triptan, <i>n</i> (%): sumatriptan 25 mg: 89 (70.1); sumatriptan 50 mg: 105 (33.3); sumatriptan 100 mg: 62 (27.2); sumatriptan nasal spray: 17 (37.7); sumatriptan SC: 10 (12.2); zolmitriptan: 69 (28.9); rizatriptan: 52 (26.7); naratriptan: 54 (39.4)</p> <p>*Incomplete or no relief were most common most frequent switches in 6 out of the 8 assessed formulations. Side effects were the most frequent cause leading to switches in the remaining two (sumatriptan 100 mg and sumatriptan SC)*</p> <p>*Patients using sumatriptan 25 mg were more likely to report that the other triptans they used to be better, while patients using sumatriptan SC were less likely to do so. For all the other triptan/formulations, patients were equally likely, from a statistical perspective, to report that other triptan they had used was better. More patients who used sumatriptan 50 or 100 mg as the initial triptan were likely to switch back to it*</p>

Table 2 continued

Author, year	Study design	Patient population; characteristics investigated	Study description or intervention	Results (key relevant findings)
Alam, 2018 [72]	Cohort study: Web-based survey	Respondents using acute prescription migraine medications	Any triptan Overall triptan use and discontinuation with oral/nasal/injectable triptan	Discontinuation rates were highest for injectables (81.5%), nasal sprays (66.5%), and oral medications (55.2%) Lack of efficacy and side effects were the main reasons for discontinuation

b hour, *SC* subcutaneous

Three studies investigating subsequent responses to a higher dose and/or alternative formulation of sumatriptan [24, 26, 28], and one publication describing subsequent response to combination treatment, are summarized in respective sections [29].

In addition to the ten studies described earlier, three subgroup analyses identified and assessed outcomes to subsequent acute treatments in patients with prior triptan insufficient efficacy and/or tolerability from a broader group of patients within RCTs; subsequent treatments investigated were telcagepant, zolmitriptan, ubrogepant, and lasmiditan [31–33]. In the analysis assessing outcomes with telcagepant and zolmitriptan, percentage of patients with historical poor triptan response or no triptan use experiencing pain freedom at 2 h was 13% with telcagepant 150 mg, 14% with zolmitriptan 5 mg, 29% with telcagepant 300 mg, and 12% with placebo [31]. The therapeutic benefit of lasmiditan versus placebo for the outcome of pain-free response at 2 h was generally unaffected by prior response to triptan therapy [33]. Response rates for 2-h pain freedom were higher for ubrogepant versus placebo, and the magnitude of benefit was similar across triptan-responder, triptan-insufficient responder, and triptan-naïve patient categories [32].

Early Intervention with a Different Triptan

In two studies, in patients with reported prior triptan insufficient efficacy and/or tolerability, efficacy to a different orally administered triptan as monotherapy was assessed when treatment was administered early (e.g., within 1 h of attack onset) and/or while headache severity was still mild [25, 27]. Across these studies, pain freedom at 2 h was experienced by 30% of patients who took eletriptan 40 mg, and in 45% (zolmitriptan 5 mg) to 58% (rizatriptan 10 mg) of attacks. Pain relief at 2 h was experienced by 64% of patients who took eletriptan 40 mg, and in 73% (zolmitriptan 5 mg) to 81% (rizatriptan 10 mg) of attacks.

Higher Dose and/or Alternative Triptan Formulation

In four studies conducted in patients with prior triptan insufficient efficacy and/or tolerability, efficacy with a higher dose (sumatriptan 100 mg standard oral formulation) and/or alternative triptan formulation [rizatriptan 10 mg ODT, sumatriptan 100 mg rapid release, sumatriptan 6 mg subcutaneous (SC)] was assessed. Pain freedom at 2 h was reported in (a) up to 61% of

Table 3 Terminology and definitions used by RCTs and open-label studies to denote insufficient efficacy and/or tolerability to triptans

Study	Terminology	Definition
Previous insufficient efficacy and/or tolerability to triptans		
Inadequate/unsatisfactory response		
Stark, 2000 [23]	Patients who “respond poorly” to oral administration of sumatriptan	Patients described themselves as experiencing an unsatisfactory response to sumatriptan
Goldstein, 2006 [27]	Patients with previous “unsatisfactory response” to rizatriptan	Patients who were dissatisfied with their previous treatment response to rizatriptan within the past 12 months, due to inadequate relief from migraine headache pain; slow onset of migraine pain relief; inadequate relief from associated migraine symptoms (nausea, vomiting, phonophobia, photophobia, etc.); recurrence of migraine headache and/or needed to take multiple doses of medication to keep the pain away; delayed return to normal function; lack of consistent response; troublesome side effects
Newman, 2008 [26]	Patients previously “dissatisfied” with sumatriptan in any formulation at a dose lower than 100 mg, and had not received treatment with sumatriptan at the 100 mg dose prior to start of study	Satisfaction was measured by a single-item question with a 7-point response scale. Subjects who were dissatisfied with previous sumatriptan and were less than very satisfied with their current treatment were included in the study
Brandes, 2009 [63]	“Difficult-to-treat” menstrual migraine	Difficult-to-treat menstrual migraine was defined as having previous exposure to non-triptan therapy for the treatment of menstrual migraine and an inadequate response to triptan therapy for the acute treatment of menstrual migraine over ≥ 2 menstrual cycles An inadequate response to triptan therapy was determined by the investigator using the Migraine Medication History Questionnaire and defined as a lack of efficacy or poor tolerability, triptan dose in excess of the maximum recommended amount, the need to use rescue medication, recurrence of headache (within 48 h), or partial response

Table 3 continued

Study	Terminology	Definition
Seeburger, 2011 [20]	Sumatriptan “non-responders”	Eligible participants reported that they did not respond to treatment with sumatriptan and, at a minimum, that they have demonstrated a $\geq 50\%$ unsatisfactory response (e.g., no pain relief at 2 h post dose) to sumatriptan across their total migraine history (including failure to respond to at least 2 administrations of sumatriptan)
Discontinuation reasons		
Farkkila, 2003 [22]	Patients with previous “poor response/tolerance” to oral administration of sumatriptan	Patients who had discontinued therapy with orally administered sumatriptan between 2 weeks and 2 years prior to the screening visit. Subjects had been in the practices of the investigators for a significant period and their lack of enough response to sumatriptan was documented in the patient notes. Patients were asked to give one of the following reasons for stopping treatment with sumatriptan: slow onset of action; inconsistent response; poor overall efficacy; recurrence; tolerability
Mathew, 2009 [29]	“Poor responders” intolerance to short-acting triptans	Poor response was defined as patient-reported discontinuation of treatment with a triptan for reasons related but not limited to slow onset of efficacy, inconsistent efficacy, poor overall efficacy, or poor sustained efficacy through 24 h or longer Intolerance was defined as discontinuation of treatment with a triptan for any reason other than poor response, hypersensitivity, or allergic reaction
Considered consistency of response		
Mathew, 2000 [25]	Oral administration of sumatriptan “non-responders”	Defined as lack of response in at least 3/5 attacks having taken the medication early in the headache phase ^a
Landy, 2004 [24]	Patients with a history of “non-response” to sumatriptan 50 mg	Patients had a documented history of non-response to 50 mg sumatriptan tablets at 2 h after dosing in the early, mild-pain phase of 2/3 migraine attacks ^a
Diener, 2005 [21]	Patients with previous “poor response” to sumatriptan 50 mg	Patients describing themselves as experiencing an unsatisfactory response to sumatriptan on ≥ 2 prior occasions ^a

Table 3 continued

Study	Terminology	Definition
Diamond, 2007 [28]	Patients who historically “fail to respond” to orally administered triptans	Patients with migraine who historically had failed to achieve relief from an orally administered triptan in 2/3 attacks. Relief was defined as reduction of pain severity from mild, moderate, or severe pain to no pain, or from moderate or severe pain to mild pain
Other		
Ho, 2011 [31]	Patients with self-reported historical triptan response of “poor/no use” ^b	<p>Patients completed a migraine history questionnaire, which included the following question to determine whether patients had insufficient efficacy to triptans: “On average, how often did your moderate or severe migraine headaches respond to triptan medications?”</p> <p>Patients had to select from 75–100% of the migraine attacks (good triptan historical response subgroup); 50–74% of the migraine attacks; 25–49% of the migraine attacks (intermediate triptan historical response subgroup); < 25% of the migraine attacks; you do not take triptans (poor/no historical triptan response subgroup); take triptans but do not know the frequency of response (excluded)</p>
Kniewel, 2018 [33]	“Non-responders” to triptan therapy	At baseline, patients rated themselves as good, poor, or non-responders to prior triptan therapy ^a
Blumenfeld, 2019 [32]	Triptan “insufficient responder”	Patients were categorized on the basis of historical experience as a triptan-responder, triptan-insufficient responder, or triptan-naïve. Reasons for categorization as insufficient considered efficacy, tolerability, and contraindications or warnings ^a
Insufficient efficacy and/or tolerability to triptans in a general population of patients with migraine		
Cady, 2007 [35]	“Lack of response”, “non-responders”	Non-responders failed to meet endpoints “freedom from pain” at 2 h post dose, and 24 h “sustained freedom from pain”, and were permitted to use rescue medication 2 h post dose
Cady, 2014 [65]	“Non-responders”	Non-responders failed to meet the endpoint “mild or no pain 2 h post dose” without the use of a rescue medication or an increase in pain level within 24 h of treatment

Table 3 continued

Study	Terminology	Definition
Diener, 2008 [45]	High risk of “non-response”	Patients at high risk of non-response were identified on the basis of a logistic regression analysis, using 3 predictors of not achieving a 2 h pain-free response: severe baseline headache pain; photophobia/phonophobia; nausea
Landy, 2014 [66]	Headache “non-responders”, pain-free non-responders	Headache non-response at 2 h or sustained at 24 h, defined by failing to experience a 2-point reduction in a 4-point scale of pain intensity at 2 h or 24 h, respectively Pain-free non-response at 2 h or sustained at 24 h, defined by failing to achieve intensity of “no pain”
Miljkovic, 2018 [70]	“Failure” of therapy	Patients who failed to achieve complete reduction of migraine pain 2 h post dose
Scott, 1996 [64]	“Non-responders”	Patients failed to meet the endpoint “headache relief/freedom” in response to sumatriptan within 4 h of taking second dose
Spierings, 2009 [67]	“Non-response”	Patients who did not respond to frovatriptan treatment within 2–24 h post dose
Tietjen, 2005 [34]	“Inadequate relief”, “not satisfied”	Patients who had achieved (self-defined) meaningful relief and whether they were satisfied with naratriptan 2.5 mg

b hour

^a Further objective criteria were not provided

^b A limitation of this study was that this subgroup of patients comprised mainly (91%) patients who reported that they did not take triptans, but it was not known whether these patients were triptan-naïve or had discontinued treatment with triptans

patients treated orally with sumatriptan 100 mg rapid release, in participants dissatisfied with sumatriptan at a dose less than 100 mg [26], (b) 80% of attacks treated with sumatriptan 100 mg standard formulation in participants with non-response to sumatriptan 50 mg [24], and (c) up to 56% of patients treated with sumatriptan 6 mg SC in participants who had failed to respond to an orally administered triptan [28]. The study assessing rizatriptan 10 mg ODT is described in an earlier section along with the other two studies that included a run-in validation phase [20].

Combination Therapy in People with Insufficient Efficacy and/or Tolerability to Triptans

Three crossover studies investigated efficacy of combination treatment in patients who reported insufficient efficacy and/or tolerability to an orally administered triptan alone [29, 34]. Two were identical studies in patients who had discontinued a short-acting triptan and subsequently used an orally administered combination of sumatriptan 85 mg plus naproxen 500 mg. Sumatriptan plus naproxen

Table 4 Terminology and definitions used by observational studies to denote insufficient efficacy and/or tolerability to triptans

Study	Terminology	Definition
Historical insufficient efficacy and/or tolerability to triptans		
Inadequate/unsatisfactory response		
Sarchielli, 2006 [38]	“Non-responders” to rizatriptan	Patients were selected on the basis of a poor response to rizatriptan. Inefficacy was verified in the treatment of at least 3 consecutive attacks using the following definition: failure to achieve a reduction in pain from severe or moderate to mild or absence of pain within 2 h after rizatriptan administration, without a recurrence in the next 48 h
Discontinuation reasons		
Sheftell, 2004 [68]	Patients who were currently using a triptan as acute treatment medication for migraine and who had previously used at least one other triptan or a different triptan formulation	For each triptan/formulation used, information regarding patients’ satisfaction and reasons for discontinuation were summarized in following categories: to determine if another triptan is better; recurrence; incomplete/no relief; side effects; rebound; another triptan/formulation used was better; time to relief; other
Other		
Silberstein, 2019 [37]	Triptan “insufficient responder”	Patients currently prescribed triptans/had received triptans in the past 6 months and failed to achieve pain freedom at 2 h, or discontinued because of lack of efficacy/side effects
Insufficient efficacy and/or tolerability to triptans in a general population		
Alam, 2018 [72]	Discontinued triptan users	Assessed reasons for discontinuation from a pre-coded list of side effects and triptan sensations
al Deeb, 1997 [69]	“Poor or nil response” (and poor efficacy)	A poor response to sumatriptan was characterized by a drop of no points, operationalized on the basis of pain diminution along a pain severity scale
Linder, 1996 [71]	No response or “suboptimal response”	Lack of efficacy defined by failing to meet the endpoint “headache relief”
Munjal, 2016 [36]	“Inadequate pain response”	Patients who responded “never, rarely and less than half the time” when asked if they achieved the endpoint “pain freedom” at 2 h and “24 h sustained relief”

Table 4 continued

Study	Terminology	Definition
Patrick, 2000[39]	“Non-responders”	Treatment response to the initial zolmitriptan dose was assessed at 2 h using the following endpoints: headache response, pain-free response, and improvement in impairment of normal activity. Patients also recorded whether they had obtained meaningful migraine relief, a subjective global evaluation of treatment response incorporating all migraine symptoms, within 2 h of dose administration. Non-responders were defined as patients with a response rate of 0–10%
Peng, 2016[40]	“Non-responders”	Patients were asked the effectiveness and AEs of one sumatriptan tablet for their migraine attack; however, non-response was not defined by the authors
Seo, 2016[41]	Frovatriptan “inefficiency”	Patients failed to meet the endpoint “pain relief or absence” 4 h post dose in 1 of 2 successive migraine attacks
Sheftell, 2010[42]	“Dissatisfied”, non-responding headaches	Secondary treatment failure was defined as a return of pain to any level following initially successful treatment
Terrazzino, 2010[43]	“Inconsistent response”	Patients who did not experience a ≥ 2 -point reduction in a 4-point scale of pain intensity 2 h post dose in at least 2 out of 3 attacks
Wang, 2017[44]	“Non-responders”	Patients who reported no response/effectiveness based on the endpoint “freedom from pain, or reduction to mild intensity in headache severity” within 2 h post dose in at least 2 of 3 migraine attacks

AE adverse event, *h* hour

was superior to placebo for pain freedom at 2 h (40–44% vs. 14–17%) and sustained pain freedom 2–24 h (26–31% vs. 8%) [29]. The third study investigated efficacy of orally administered naratriptan plus rectally administered prochlorperazine in patients with insufficient efficacy to orally administered naratriptan alone. None of the 14 patients who received this combination reported being pain-free at 2 h and the authors concluded that there was no

evidence of benefit by adding prochlorperazine rectal suppository to naratriptan [34].

Treatment of Patients with Allodynia

Two studies identified in this SLR investigated triptan efficacy in patients with migraine with baseline allodynia or symptoms of subcutaneous sensitivity (SCS). In one study, pain freedom at 2 h with rizatriptan 10 mg,

administered within 1 h of onset while pain was mild, ranged from 55% to 59% across patients both with and without baseline SCS [35]. At 2 h post dose, treatment with rizatriptan versus placebo led to significantly larger reductions in proportions of patients with SCS. The presence of SCS at time of dosing was not predictive of pain freedom at 2 h; however, presence of SCS at 2 h correlated with lack of pain freedom at 2 h [35]. In the American Migraine Prevalence and Prevention (AMPP) study, in which medication was taken earlier in the course of attacks compared to most clinical trials, lack of pain freedom at 2 h in at least half of the attacks was reported more often in triptan users with allodynia (50%) versus those without allodynia (36%) [36].

Characteristics Potentially Associated with Insufficient Efficacy and/or Tolerability to Triptans

Several observational studies investigated potential predictors and characteristics associated with triptan insufficient efficacy and/or tolerability [36–44]. In addition to those observational studies, two subgroup analyses from RCTs investigated predictors of insufficient efficacy within a single attack [35, 45].

Study participants with insufficient efficacy and/or tolerability to triptans were more likely to be younger [40, 41, 44], of female gender [40, 42], and have clinical depression or have more symptoms of depression [36, 40, 41, 44]. Additionally, patients with triptan insufficient efficacy and/or tolerability commonly presented with more severe baseline headache intensity [36, 40, 42, 45], higher headache frequency [36, 44], baseline photophobia, phonophobia, and/or nausea [24, 29, 40, 42, 44, 45], presence of allodynia [36], and were less likely to be on migraine preventive medications [36, 43]. It is not clear from the conference abstract if the timing for presence of allodynia was at time of dosing or over patients' lifetime [36].

Two studies identified that regular coffee consumption is associated with effectiveness of sumatriptan [40, 44]. One study showed that

patients with a polymorphism in serotonin transporter gene were more likely to experience inconsistent response to a single triptan, as measured over three attacks [43]. Another study showed that insufficient efficacy to rizatriptan was correlated with lesser degree of trigeminal activation and lower variations of trigeminal neuropeptides after triptan administration [38]. Other studies showed that patients with triptan insufficient efficacy and/or tolerability were more likely to have higher opioid use, utilize a higher level of healthcare resources, have more rebound headaches, and have worse migraine-specific quality-of-life assessments [37, 39].

DISCUSSION

This comprehensive literature review identified substantial variability in methodology and definitions involving triptan insufficient efficacy and/or tolerability and focused on extracting clinically relevant evidence to provide value for clinicians and ultimately patients.

Definitions to identify patients with triptan insufficient efficacy commonly involved lack of pain freedom at 2 h and pain relief at 2 h in a single attack. For both outcomes, some definitions further included qualifiers such as achieving outcome over at least two out of three attacks. Some studies relied on prior discontinuation while others were purely subjective self-assessments based on treatment satisfaction. Several studies applied definitions that allowed for either efficacy or tolerability; none applied a definition specific only to tolerability.

The totality of evidence indicates that some people with insufficient response/tolerability to one triptan may benefit from switching to a different triptan. Switching studies that validated prior insufficient efficacy and/or tolerability to sumatriptan showed that approximately two-thirds of the participants did not experience pain relief at 2 h when re-challenged with sumatriptan within the trials [20, 21, 23]. In those studies, approximately 25–50% of patients subsequently experienced pain relief at 2 h with a different triptan. In studies that did not have a run-in validation period, up to two-thirds experienced pain relief

at 2 h after subsequent treatment with a different triptan [25, 27, 30]. In two studies that specified early administration of a different oral triptan monotherapy, rates of pain freedom and pain relief at 2 h were relatively high compared to studies that did not treat early [25, 27].

None of the studies investigated subsequent outcomes in patients who had only triptan insufficient tolerability apart from those who had insufficient efficacy. A remaining unresolved question involves how many patients would benefit from a third triptan after failure to respond to an initial two triptans. Data from a claims database study showed that 8% of patients who initiated a triptan had at least three acute treatment changes (not specific to triptans) over a 1-year period [46]. However, none of the studies identified in this SLR assessed outcomes associated with three or more acute treatment changes.

Some studies identified here demonstrated benefit with a higher dose (sumatriptan 50 mg to 100 mg) or different formulation (sumatriptan rapid release, sumatriptan SC, rizatriptan ODT) of a triptan. Some identified benefit by adding a non-steroidal anti-inflammatory drug (NSAID). The combination of a triptan with an NSAID is recognized as a strategy for triptan insufficient efficacy in Canadian, French, German, the UK, and EHF treatment guidelines [47–51].

Terminology commonly used in studies included non-response or non-responder. However, those terms do not offer clear context as to whether the non-response refers to efficacy, tolerability, or both. In addition, lack of optimal response in these patients could be perceived as being a reflection of the patient rather than the treatment. It seems more accurate and empathetic to refer to “efficacy”, “tolerability”, or when not known (which is often the case), “efficacy and/or tolerability” when referring to patients experiencing insufficient response associated with treatment.

This review found that patients with triptan insufficient efficacy and/or tolerability were more likely to have more frequent and severe headaches; were more likely to have baseline photophobia, phonophobia, nausea, and allodynia; and were less likely to be on preventive

medications or have regular caffeine intake. Additional studies have corroborated many of these predictors, especially with regard to higher severity of baseline pain, presence of nausea, and presence of photophobia or phonophobia [52, 53]. Some studies showed that patients in this population were more likely to be younger, female, and more likely to have signs of depression. Potential reasons could include that younger patients may have less experience with the natural history of migraine and with managing their individual attacks, and migraine attacks associated with menstruation may be more difficult to treat [54].

Insufficient response to triptans has been shown to result in considerable humanistic burden [55–57]. While effective for many, the unmet need remains high in patients using triptans, resulting in the need for newer drug classes [58, 59]. With novel acute treatments emerging, however, the future algorithm for the acute treatment of migraine is not yet established. This includes guidance on the point at which switching to a different medication class should be considered. In the USA, the AHS has recently published a position statement regarding patients who have contraindications to triptans or who have failed to respond or tolerate at least two orally administered triptans. The statement recommends that these patients would be eligible for one of the new acute treatments, namely lasmiditan, ubrogepant, rimegepant, or neuromodulation device [1]. A recently published article not identified in this SLR, provides the response rates for lasmiditan versus placebo in patients who reported good and insufficient response to prior triptan therapy; efficacy was similar across these patient categories [60]. It may become clinically relevant to understand whether response rates of new treatments would be different in people with contraindications to triptans who immediately initiate new novel treatments versus those who have two prior triptan failures.

Increased physician awareness may help better identify patients at risk of insufficient response to triptans [55]. In addition to factors identified here, overuse of over-the-counter (OTC) medication and timing of triptan

administration were factors identified in a global real-world study using data obtained from physicians and patients. Patient-Reported Outcomes (PROs) are mostly used in clinical research rather than in clinical practice. However, some PRO tools such as Migraine-Specific Quality of Life Questionnaire (MSQ) and Migraine Disability Assessment (MIDAS), although not specific to acute treatment, might give an idea of impact of attacks [55]. Further, it might be helpful to have some potential specific PRO tools such as Migraine Treatment Optimization Questionnaire (MTOQ) for the acute treatment which may aid physicians in identifying when to consider reassessment of migraine treatment options [55].

Strengths of this review include application of an up-to-date, rigorous systematic and comprehensive approach to identify all published studies in which the population of patients with triptan insufficient efficacy and/or tolerability was specifically assessed. Limitations include the selective use of published data, inclusion of only publications reported in English, and small numbers of patients in several studies. The design characteristics and statistical limitations of the identified studies have the potential to introduce inherent biases and lack validation. As a result of the heterogeneity and lack of uniformity across studies, results from this review are presented as a narrative synthesis without any comparisons across studies. Reliance on retrospective PROs, recall bias, and inter-subject variability also may have affected the findings. Within studies, besides the methodological limitations, there are some other plausible reasons that may contribute towards insufficient response to orally administered triptans including limited bioavailability and the impact of nausea and vomiting [53, 61]. These factors vary between individuals and orally administered triptans. This may make it difficult to assess true treatment failure rates, especially if a single attack is studied.

Several studies identified here did not apply a paradigm of early treatment that may influence their results and clinical interpretation. The importance of treating migraine attacks with triptans early and/or while headache severity is mild has been demonstrated in various studies,

including the foundational “Act when Mild” study [62]. In clinical practice, patients may treat subsequent attacks earlier on the basis of personal experience. Also, given the variable characteristics of migraine treatments, there could be a learning curve when switching acute treatments. This learned behavior is likely to be associated with increased efficacy.

CONCLUSIONS

This compilation of results supports the assertion that a large unmet need remains in the acute treatment of migraine. Regardless of the methodologies or definitions applied across studies, a sizeable proportion of patients did not have optimal outcomes to subsequent treatment or strategies. Solutions to improve the management of those impacted could include increased patient and physician education, increased awareness of treatment optimization strategies, and availability of additional treatment options. Future studies can focus on prediction analyses using real-world data such as pharmacy databases to explore best possible treatment options for those with insufficient responses to triptans [58].

An increased level of consistency in defining insufficient efficacy could help identify patients who have the most potential to benefit from optimization of currently available treatments or availability of newly emerging acute treatments.

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Data Availability. All data generated or analyzed during this study are included in this published article/as supplementary information files.

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