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Review

Comparison between metamizole and triptans for migraine treatment: a systematic review and network meta-analysis

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Abstract

Objective
The aim of this systematic review was to evaluate the efficacy of metamizole and triptans for the treatment of migraine.

Methods
Randomized controlled trials including people who received metamizole or triptan by multiple routes of administration and at all doses as treatment compared to subjects who received another treatment or placebo were included in the systematic review. The primary outcomes were freedom from pain at 2 hours; pain relief at 2 hours; sustained headache response at 24 hours; sustained freedom from pain at 24 hours. The statistical analysis of all interventions of interest were based on random effect models compared through a network meta-analysis.

Results
209 studies meeting the inclusion and exclusion criteria were analyzed. Of these, 130 had data that could be analyzed statistically. Only 3.0% provided enough information and were judged to have a low overall risk of bias for all categories evaluated; approximately 50% of the studies presented a low risk of selection bias. More than 75% of the studies presented a low risk of performance bias, and around 75% showed a low risk of detection and attrition bias.

Conclusion
There is no evidence of a difference between dipyrone and any triptan for pain freedom after 2 hours of medication. Our study suggests that metamizole may be equally effective as triptans in acute migraine treatment.

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Introduction

Migraine is a highly prevalent condition manifesting as moderate or severe intermittent headache attacks with associated symptoms, lasting 4 to 72 hours if not properly treated.[1-3]

Migraine is not only a headache but also a syndrome of various phases, each with its own distinct mechanisms and treatment approaches. Briefly, the migraine prodrome, or premonitory phase, can occur several hours to days before a headache and may be hypothalamically modulated, although other brainstem and limbic structures may play a causal role as well.[4]

The relationship between migraine and cognition is complex. Cognitive symp-toms are part of the subjective experience of migraine attacks and contribute to attack-related disability, interfering with work performance, family and social life, besides self-management of the attacks. This transient impairment may occur along all phases of a migraine attack. While pain is the main determinant of disability, cognitive dysfunction also contributes to attack-related impairment, and should be considered as a migraine therapeutic target, together with pain, to evaluate the efficacy of an acute attack treatment.[5]

While it is clear that migraine attacks include some degree of cognitive impair-ment, in the long run, migraine is not associated with any significant impact on cognitive performance or age-associated cognitive decline in the general popu-lation. So, acute cognitive dysfunction during a migraine attack is reversible. However, individuals with more severe and frequent migraine attacks and sub-jects with chronic migraine tend to maintain cognitive difficulties between at-tacks.[5]

The acute management of migraines includes the use of non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, metamizole, ergots, and triptans. Gepants and ditans have been recently added to the list.[6]

Metamizole is a well-established and highly used drug to treat acute attacks in emergency settings in Brazil, as well as the most common analgesic medication used for migraine treatment in the population.[7,8]

Triptans represent a large therapeutic group with a good therapeutic profile, but their vasoconstriction adverse events warrant caution in patients with cardio-vascular risk. Other side effects, such as nausea, dizziness and chest symp-toms, preclude some patients from using triptans, while a few patients do not respond well to triptans. Compliance and tolerability of triptans are certainly different for each medicine. Triptans are considered to be safe, with a very low potential risk of clinically significant serious adverse events. Contraindications to triptan use include uncontrolled hypertension, ischemic heart disease, coronary vasospasm, cerebrovascular disease, peripheral vascular disease, and basilar or hemiplegic migraine.[9, 10]

Metamizole and triptans are both major medications in the acute therapy arse-nal, however, they have never been directly compared.

To evaluate the efficacy of metamizole and triptans for the treatment of migraine, we conducted this systematic review and network meta-analysis to address the following focused questions: (1) "what is the evidence for the efficacy and safety of metamizole for the treatment of migraines compared with triptans?" and (2) "how effective are those treatments in improving cognitive dysfunction in patients with migraine?"

Methods

TThe systematic review has been developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA) statement[11-13], using methodology described in the Cochrane Handbook for Systematic Review of Interventions.[14] This protocol was registered within the PROSPERO database (CRD42020216360).

Study eligibility criteria

Only randomized controlled trials reporting study-specific data for migraine outcomes in people who received metamizole or triptan as treatment were included in the systematic review. The population of interest was participants with migraine, of any age, gender and severity of migraine. We have used investigator-reported definitions (according to accepted diagnostic criteria, such as the International Classification of Diseases, or according to the criteria established by the International Headache Society).[15] We examined papers from all countries, subjects who have used metamizole or triptan treatment (test group), by multiple routes of administration (tablets, oral disintegrating tablets, injection, transdermal, nasal spray, rectal suppositories) and at all doses (any frequency or strength), compared to subjects who have

received another treatment or placebo. Metamizole and Triptans were not allowed to be used in combination with other drugs. The primary outcomes were freedom from pain at 2 hours; pain relief at 2 hours; sustained headache response at 24 hours; sustained freedom from pain at 24 hours. Secondary outcomes were relief of other symptoms associated with migraine, specifically nausea, vomiting, photophobia and phonophobia, fatigue, dizziness, cognitive impairment, any adverse effects (AEs), withdrawals due to adverse events, use of rescue medication, patient satisfaction, absenteeism, functional disability and quality of life.

We excluded studies in which metamizole or triptan was not the intervention of interest, studies comparing combined metamizole preparations with another treatment, studies comparing combined triptan preparations with another treatment, studies where metamizole or triptan have not been studied in only one separate intervention group, studies in which migraine is not reported as the outcome of interest, studies that do not have adequate information regarding whether metamizole or triptan and its derivatives are not related to migraine improvement, studies involving secondary headache disorders (post-puncture headache, post-traumatic headache, cancer-related headache etc.), studies that do not have adequate information on the classification of primary headache or animal studies. There was no restriction of study setting.

Information sources

We searched the literature in the following databases: MEDLINE via PubMed, EMBASE, LILACS, EbscoHost and all references of the included studies, with no language restrictions from inception to November 2020. MesH terms and keywords were combined with Boolean operators and used as search strategies: #1 - migraine OR headache OR "tension-type headache"; #2 - dipyrone OR metamizole; #3 – triptan OR sumatriptan OR zolmitriptan OR rizatriptan OR naratriptan OR frovatriptan OR almotriptan OR eletriptan; #4 - #1 AND #2; #5 - #1 AND #3; #6 - #4 OR #5. Two reviewers screened all articles identified from the search independently. Any disagreements between reviewers were solved by discussion with a third reviewer to meet a consensus. Studies meeting the inclusion criteria underwent a validity assessment and data extraction. Reasons for rejecting studies were recorded for each study.

Data extraction (study characteristics and results) / Data management

Two reviewers extracted data independently. Disagreements were solved with discussion with a third reviewer. Data were transferred to Excel sheets for analysis. Measures of central tendency (mean or median) and dispersion (standard deviations and percentiles) for different biometric parameters were extracted. For continuous outcomes, the following was extracted: means, SD and sample sizes at baseline and follow-up. If these were unavailable, change scores or mean differences were extracted. For dichotomous outcomes, the number of cases and total sample size were extracted. Safety outcomes included the number of participants reporting any or serious AEs or withdrawn from the study because of AEs.

All interventions of interest were compared through a network meta-analysis. A graph summarized the results of interest, allowing us to easily assess the structure of existing evidence.

Risk of bias within individual studies

The risk of bias of the included studies was evaluated according to the Cochrane Collaboration's Tool for Assessing Risk of Bias.[14] Briefly, randomization and allocation methods (selection bias), completeness of follow-up period/incomplete outcome data (attrition bias), masking of patients (performance bias) and examiners (detection bias), selective reporting (reporting bias), and other forms of bias were classified as adequate (+), inadequate (-), or unclear (?). Based on these domains, the overall risk of bias was categorized as follows: 1) low risk of bias; 2) unclear risk of bias; or 3) high risk of bias.

Summary measures

To inform on comparative efficacy, effectiveness, and safety between all interventions, we conducted a network meta-analysis. We modeled log odds ratios using the conventional logistic regression network meta-analysis setup.[16] The network meta-analysis was based on logistic model with random study effects.[17]

Assessment of inconsistency

Consistency was assessed by comparison of the conventional network meta-analysis model for which consistency was assumed with a model that does not assume consistency (a series of pairwise meta-analyses analyzed jointly). If the trade-off between model fit and complexity favors the model with assumed consistency, this model was preferred. Moreover, we calculated the difference between direct and indirect evidence in all closed loops in the network; inconsistent loops were

identified with a significant (95% CI that excludes 0) disagreement between direct and indirect evidence.

Risk of bias across studies

Publication bias or small study effects were assessed by inspection of the funnel plots for asymmetry and with Egger's test[18] and Begg's test[19], with the results considered to indicate potential small study effects when $p<0.10$.

Results

The search identified 4,003 articles. After excluding duplicate references, a total of 1,601 titles and abstracts retrieved from electronic databases and hand searching were analyzed. Based on the eligibility criteria, the texts of 450 publications were reviewed in full. Of these, 198 were eligible according to the inclusion and exclusion criteria (see Figure 1). Ten articles published results from more than one study, thus 209 studies were analyzed.[20-29]

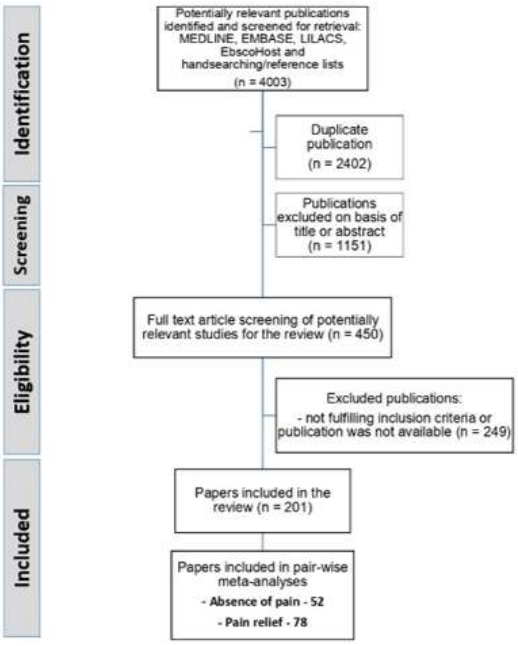


Figure 1. Diagram.

All of the included studies were published between 1991 and 2019. Most of them were large, multicenter, double-blind, placebo-controlled trials conducted in a variety of countries in the five continents.

The number of randomized patients who received some treatment totaled 94,570 subjects, diagnosed with migraine headaches according to the International Headache Society criteria for migraine. Excluding four studies that did not mention participants' sexes30-33, female participants were the majority, with approximately 84.2%.

The types of treatments varied widely both in dosage and route of administration. The seven types of triptans (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan) appeared among the selected studies. However, sumatriptan was the most common and was found in 18 different variations: it appeared with oral, subcutaneous, nasal spray, iontophoretic transdermal patch (TDS) and suppository administration, combining dosages from 1 mg to 200 mg.

Some treatment arms used triptan in combination therapies with other drugs: frovatriptan 2.5 mg + dexketoprofen 25 mg or 37.5 mg[34]; naratriptan 2.5 mg orally + rectal suppository of prochlorperazine 25 mg[35]; rizatriptan 10 mg + acetaminophen 1,000 mg orally[36], and rizatriptan 10 mg + dexamethasone 4 mg orally[37]. All studies with combination therapy included in this review had an exclusive triptan arm and a placebo comparative arm.

Only 6 studies with metamizole to treat migraine (dosage of 500 mg and 1,000 mg orally and IV) met all the inclusion criteria to be considered in this systematic review. Four studies utilizing the intravenous metamizole route were performed in Brazil[8,38-40], one in Spain[41] and the last one in Turkey[42,43], with the last two studies including oral metamizole.

Most studies included in this review were conducted in the adult population and only 13 were carried out with adolescents.[43-55]

Most of the selected studies evaluated improvement or complete relief of headache after 1 hour, 2 hours and in the first 24 hours, although some studies have evaluated different times of symptomatic relief after 30 minutes, in addition to the use of rescue medication in the period. Some studies have evaluated relief of migraine-associated symptoms, such as photophobia, phonophobia, nausea and vomiting. The characteristics of the included studies is in supplementary table (Table 1).

The results of the risk of bias assessment are shown in figure 2. Of all 209 studies, only six (3.0%) provided enough information and were judged to have a low overall risk of bias for all categories evaluated; 146 studies had insufficient information, mainly in the selective reporting domain, so the overall risk of bias was unclear, and 46 presented a high overall risk of bias.

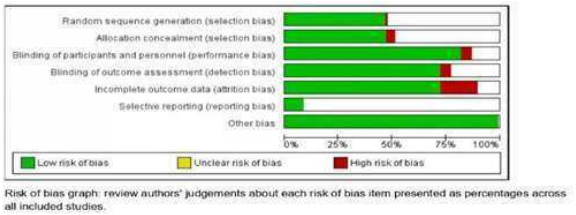


Figure 2. Risk of bias graph: review authors' judgements about each domain presented as percentages across all included studies.

Approximately 50% of the studies presented a low risk of selection bias. More than 75% of the studies presented a low risk of performance bias, and around 75% have shown a low risk of detection and attrition bias.

The statistical analysis below was based on random effect models from network meta-analyses. The calculations were made with the netmeta package of the R library, developed by Rücker et al.[56] and based on the methodology described in Schwarzer et al.[57]

Since there are no direct comparisons of dipyrone versus any of the triptans, consistency tests were not performed.

Pain freedom after 2 hours of medication

Figure 3 illustrates the connections between the active substances. The thickness of the edges indicates the weights of the direct comparisons. Studies with more than two treatments were excluded in this analysis.[20,36]

There is no evidence of a difference between dipyrone and any triptan.

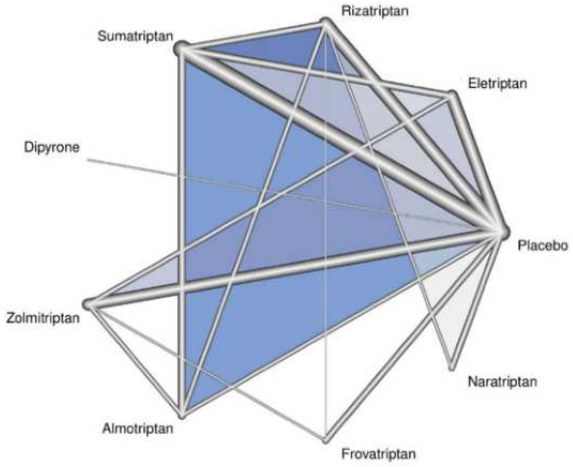


Figure 3. Network graph for pain-free data after 2 hours of medication.

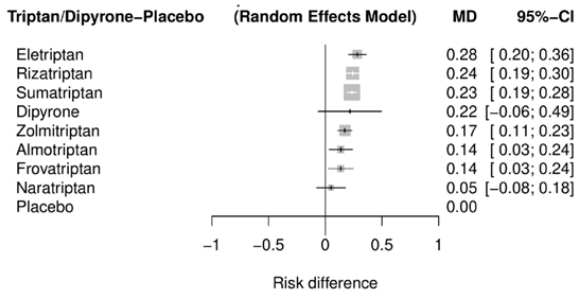


Figure 4. Estimates of the effect of triptans and dipyrone in relation to placebo.

Pain relief after 2 hours of medication

Figure 5 illustrates the connections between the active substances.

The confidence intervals for differences in pain relief ratios after 2 hours of medication between triptan and placebo versus dipyrone are shown in the forest plot. There is no evidence of a difference between dipyrone and any triptan.

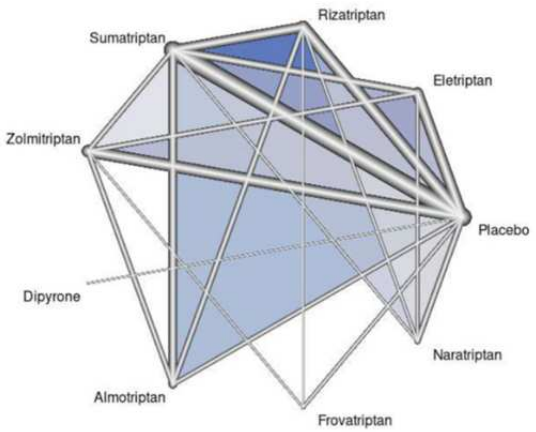


Figure 5. Network graph for pain relief data after 2 hours of medication.

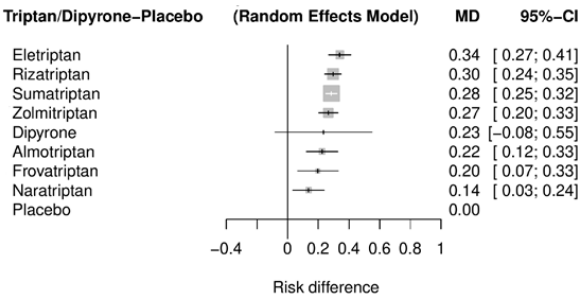


Figure 6. Estimates of the effect of triptans and dipyrone in relation to placebo.

Table 1. Characteristics of Included Studies

Author, publication year	Population	Comparisons	Outcomes
Ahonen et al.[44]	Children/Adolescents - 12.4 (SD 2.4, range 8.1 to 17.5) years n=94 (51 boys and 43 girls)	Sumatriptan 10 mg (20 to 39 kg) Sumatriptan 20 mg (≥40 kg) Placebo A single dose of sumatriptan nasal spray and a matching placebo were administered at home during two attacks.	The primary efficacy endpoint was headache relief by two grades on a 5-grade face scale at 2 hours. Sumatriptan (n 53/83; 64%); placebo (n 32/83; 39%)
Ahonem et al.[43]	Adolescents - 12.0 years (SD 2.4; range 6.1 to 16.1 years) n=116 (63 girls and 53 boys)	Oral rizatriptan 5 mg (20 to 39 kg); Oral rizatriptan 10 mg (40 kg or more); Placebo Two doses of rizatriptan and a matching placebo were administered at home during three attacks.	Ninety-six patients used all three treatments, 10 used two, and 10 only the first. At 2 hours, the primary endpoint (headache relief by two grades on a five-grade face scale at 2 hours) was reached twice as often after both treatments of rizatriptan [first n=71/96 (74%); second n=70/96 (73%)] as after placebo [n = 35/96 (36%)] (p<0.001). Already at 1 hour, rizatriptan was clearly more effective as headache relief was reported by 50% (n = 48/96) and 55% (n = 53/96) of children after the first and the second dose of rizatriptan, compared to 29% (n= 28/96) after placebo (p=0.004). Rizatriptan was superior at 3 and 4 hours, and the other endpoints also favored rizatriptan. Efficacy of rizatriptan was constant over the two treated attacks, and the findings were similar in children using the dose of 5 and 10 mg. The use of the higher 10 mg adult dose in adolescents caused adverse effects with a frequency comparable to what has been observed in adults. But no serious adverse effects were observed.
Ahrens et al.[58]	Adults – Placebo - 41.6 (18 to 72) years; Rizatriptan 5 mg - 42.7 (19 to 67) years; Rizatriptan 10 mg 43.1 (19 to 67) years. n=555 (64 male and 491 female)	Rizatriptan 10 mg Rizatriptan 5 mg Placebo Single attack	The primary efficacy endpoint was pain relief at 2 h. From 30 min onwards, significantly more patients experienced pain relief and became pain-free after rizatriptan 10 mg compared to placebo. At 2 h, the percentage of patients with pain relief was significantly higher after rizatriptan 10 mg (74%), 5 mg (59%) compared with placebo (28%). Rizatriptan 10 mg was superior to rizatriptan 5 mg on pain relief at 1.5 and 2 h (p < 0.05). Significantly more patients were pain-free at 2 h after rizatriptan 10 mg (42%), 5 mg wafer (35%) compared with placebo (10%). Both doses of rizatriptan wafer were well tolerated.
Akpunon et al.[59]	Adults – Plac - 39.8 (SD 9.4) - 22 to 59 SUM - 39.8 (SD 10) - 22 to 71 years; n=136 (17 Male; 119 Female) Sum - Male 10 (11%); Female 78 (89%)	Sumatriptan 6 mg SC Placebo	N° of patients with meaningful relief - Plac 17 (35%); Sum 66 (75%) Time to meaningful relief (min) median- Plac 66; Sum 43 N° of patiens with nopain or mild pain at discharge - Plac 17 (35%); Sum 62 (70%) N° of patients with no pain at discharge - Plac 6 (13%); Sum 27 (31%)
Allais et al.[60]	Adults – 34.92 ± 7.99 years n=122 (all female)	Almotriptan 12.5 mg oral Placebo One single menstrual migraine attack per menstrual cycle was treated in four different menstrual cycles.	Data suggest that almotriptan shows excellent efficacy on menstrual migraine in comparison to the placebo, with a significant reduction in the percentages of suffering patients over a 2-h period of time.
Allais et al.[61]	Adults – 34.9±8.0 (18 to 50) years n=147 (all females)	Almotriptan 12.5 mg oral Placebo One tablet after pain onset during two menstrual cycle	Significantly more patients were pain-free at two hours (risk ratio [RR] = 1.81; p=0.0008), pain-free from 2-24 hours with no rescue medication or adverse events (RR = 1.94; p=0.0061) with almotriptan versus placebo. Nausea (p = .0007) and photophobia (p=0.0083) at two hours were significantly less frequent with almotriptan. Almotriptan efficacy was consistent between three attacks, with 56.2% of patients pain-free at two hours at least twice. Adverse events were similar with almotriptan and placebo.
Almas et al.[62]	Adults – eletriptan-40 mg: 41.7±10.7 years; eletriptan-80 mg: 41.7±10.3 years. n=971 (803 females and 168 males) [eletriptan-40 mg: 453 females and 86 males; eletriptan-80 mg: 350 females and 82 males;]	Eletriptan 40 mg or 80 mg Placebo four-attack consistency of response study in which three attacks were treated with ELE-40 or ELE-80, and one randomly chosen attack was treated with placebo	On a repeated measure logistic regression analysis across all treated attacks, the probability of achieving a headache response at 2 hours ranged from 71% to 74% on ELE-40 vs. 17% to 28% on placebo (p<0.0001), and from 66% to 74% on ELE-80 vs. 21% to 27% on placebo (p<0.0001). The incidence, per attack, of adverse events, was low for both ELE-40 and ELE-80. Few adverse events occurred with incidence ≥10% on ELE-40 (asthenia, 5.0%) or ELE-80 (asthenia, 10%; nausea, 5.8%). Discontinuations because of adverse events were 0.2% on ELE-40, and 1.6% on ELE-80. (ELE: eletriptan)
Banerjee, Findley[63]	Adults - 18 to 65 years (mean 35 years) n=94 (80 female; 14 male)	Sumatriptan 200 mg oral Placebo Up to three attacks	Each patient was treated for a maximum of three separate attacks of migraine with aura within a three months' period. Three attacks were treated so that we could examine consistency of response across more than one attack. For attack 1, 200 mg sumatriptan was significantly more effective, safe and well tolerated than placebo at relieving headache 2 h after treatment was given (p=0.023). In subsequent attacks, i.e. in attacks 2 and 3, there was no such significant effect of sumatriptan compared with placebo in relieving headache

Barbanti et al.[64]	Adults: 41 years [(41.5±11.9 years sumatriptan 50 mg, 39.7±10.3 years sumatriptan 100 mg, 40.6±10.3 years placebo)] n=432 (358 females and 74 males)	Sumatriptan 50 mg or 100 mg oral Placebo Single migraine attack	Normal functional ability was restored in a significantly (p<0.05) greater percentage of patients treated with sumatriptan than placebo beginning 45 min postdose for sumatriptan 100 mg and 1 h postdose for sumatriptan 50 mg. During the 24 h after initial dosing, the median (range) lost time equivalents for the combination of paid work activities and activities outside of paid work were significantly lower in the groups treated with sumatriptan (1.1 [0-10] sumatriptan 100 mg; 0.8 [0-36] sumatriptan 50 mg) compared with placebo (2.9 [0-24]) (p≤0.01 each sumatriptan group versus placebo). The corresponding mean +/- SD values for lost time equivalents were 1.9 ± 2.3 and 2.5 ± 4.7 for sumatriptan 100 mg and 50 mg, respectively, compared with 3.5 ± 4.3 for placebo.
Barbanti et al.[65]	Adults – Rizatriptan = 43.95 ± 12.24 Placebo = 41.41 ± 11.7 n=80 (13 male; 67 female)	Rizatriptan 10 mg Placebo Single migraine attack	The primary endpoints were pain freedom at 2 h and total migraine freedom (pain freedom and absence of associated symptoms) at 2 h. Pain freedom 2h - Rizatriptan 54% vs Placebo 8% (p<0.001). Migraine freedom 2h - Rizatriptan - 51% vs Placebo 8% (p<0.001) Binomial regression analysis showed that a significantly larger percentage of patients assigned to rizatriptan than to placebo reported pain freedom at 2 h post dosing (54 % [95 % CI 38, 70 %] vs. 8 % [95 % CI -1, 17 %]) (p<0.001) and total migraine freedom at 2 h post dosing (51 % [95 % CI 36, 67 %] vs. 8 % [95 % CI -1, 17 %]) (p<0.001)
Bartolini et al.[66]	Adults – 40 ± 10 years n=114 (96 female; 18 male)	Frovatriptan 2.5 mg Almotriptan 12.5 mg Treating 1–3 attacks	The primary study endpoint was the between-treatment comparison of the direction and average strength of preference at the end of the study. Preference score averaged to frovatriptan 3.1 ± 1.3 for vs to almotriptan 3.4 ± 1.3 for (P = NS); 63% of patients expressed a clear preference for a triptan (29% for frovatriptan and 34% for almotriptan, p=NS). Pain free at 2 hours post dose - frovatriptan 30% and almotriptan 32% Pain relief at 2 h post dose - frovatriptan - 54% and almotriptan - 56%
Bigal et al.[8]	Adults – Placebo MO = 29.3 years Dipyrone MO = 32.4 years Placebo MA = 28.2 years Dipyrone MA = 35.5 years n=134 (38 male; 96 female)	Dypirone - intravenous injection of 1 g dipyrone, diluted to 10 mL of 0.9% physiological saline Placebo - intravenous injection of 10 mL 0.9% physiological saline	Positive headache response was defined as a patient's pain changing from 2 or 3 to 1 or 0 after study drug at particular end points. Headache response 1h - Placebo MO - 5/30 (16.7%) vs Dipyrone MO 20/44 (65.9%) p<0.05. Placebo MA 4/30 (13.3%) vs Dipyrone MA 19/30 (63.3%) p<0.05. Pain-free 1h - Placebo MO 3/30 (10%) vs Dipyrone MO 19/44 (43.2%) p<0.05. Placebo MA 2/30 (6.7%) vs Dipyrone MA 15/30 (50%) p<0.05. Recurrence - Placebo MO 50% vs Dipyrone MO 17% p<0.05. Placebo MA 42% vs Dipyrone MA 16% p<0.05. PS: MO (migraine without aura); MA (migraine with aura)
Bigal, Bordini, Speciali[38]	Adults – Placebo 37.6 years; dipyrone: 44.2 years; n=60 (31 women and 29 men)	Dipyrone 1 g in 10 ml saline. Placebo (intravenous injection of 10 ml saline)	Patients receiving dipyrone showed a statistically significant improvement (p<0.05) of pain compared to placebo up to 30 min after drug administration. The therapeutic gain was 30% in 30 min and 40% in 60 min. The number of patients needed to be treated for at least one to have benefit was 3.3 in 30 min and 2.2 in 60 min. There were statistically significant reductions in the recurrence (dipyrone = 25%, placebo = 50%) and use of rescue medication (dipyrone = 20%, placebo = 47.6%) for the dipyrone group.
Bigal et al.[37]	Adults – 18 to 55 years n= 35 (all female)	Rizatriptan 10 mg + dexamethasone 4 mg Rizatriptan 10 mg Dexamethasone 4 mg Tablets for 6-attack crossover study. Rizatriptan (RI) and Dexamethasone (DE)	The primary endpoint of this study was 24-hour sustained relief and the secondary was 24-hour sustained pain-free. 2-24h sustained pain relief - RI+DE 81.5%, RI 62.7%, DE 33.3%. RI was superior to DE (p=0.001), and RI+DE was superior to RI (p<0.05) and DE. (p<0.001). 2-24h sustained pain-free - RI+DE 50.7%, RI 32.2% and DE 12.1%. RI+DE was superior to RI (p<0.05), and DE (p<0.001). RI was superior to DE (p<0.05). The proportion of attacks that were considered to have been satisfactorily treated with RI+DE was not significantly different to RI only (75.3% vs 69.4%). Both were superior to DE only (37.8%, p<0.01). More attacks treated with DE+RI (33.8%) were associated with side effects compared to the RI (18.6%) and DE (15.2%).
Bigal et al.[67]	Adults – Nausea at Baseline: 40.6±11.7 years; No Nausea at Baseline: 41.1±10.3 years. n=454 (386 female and 68 male)	Sumatriptan TDS 6.5 mg (iontophoretic transdermal system) Placebo TDS over a 4-hour period treating one migraine attack.	A total of 130 participants free of nausea at baseline were treated with sumatriptan iontophoretic transdermal system (TDS), while 109 participants free of nausea at baseline were treated with placebo TDS. The occurrence of TEN (treatment-emergent nausea) (over 24 hours post-treatment was significantly lower with the sumatriptan TDS than with placebo (p=0.0011). These differences were statistically significant at 1 hour (13.8% vs 9.2%, p<0.01), 2 hours (13.8% vs 4.6% p<0.001) and 3 hours (13.8% vs 8.5%, p<0.01). The efficacy of sumatriptan TDS was similar regardless of the presence or absence of nausea at baseline for all clinical parameters.

Bomhof et al.[68]	Adults – mean age 39.2 years n=522 [438 female (84%) and 84 male (16%)]	Rizatriptan 10 mg Naratriptan 2.5 mg Placebo Tablets for the treatment of a single attack.	Rizatriptan was more effective than naratriptan. Rizatriptan provided earlier headache relief than naratriptan (hazard ratio 1.62, p=0.001), acting as early as 30 min. More patients were pain free at 2 h on rizatriptan than on naratriptan (44.8 vs. 20.7%, p=0.001). Rizatriptan also provided earlier relief of associated migraine symptoms within 2 h than naratriptan and more patients had normal function at 2 h (39.3 vs. 22.6%, p<0.001). Both active treatments were effective compared to placebo.
Bousser, D'Allens, Richard[69]	Adults – Sumatriptan = 43 ± 1.4 Placebo = 39 ± 1.3 n=96 (17 male and 79 female)	Sumatriptan 6 mg SC Placebo Two consecutive early-morning migraine attacks	The primary outcome measure was headache relief. Headache relief at 2h - First attack Sumatriptan 78% vs. Placebo 28%; Second Attack - Sumatriptan 73% vs. Placebo 20% (p<0.0001). Sumatriptan was also superior to placebo for all secondary endpoints: headache relief at 1 h, pain-free rates (grade 0) at 1 and 2 h, use of a second injection of the study treatment, use of rescue medication, duration of inability to work.
Brandes et al.[70]	Adults – mean age 39 years n=613 (484 female and 129 male)	Eletriptan 20 mg Eletriptan 40 mg Placebo to treat one attack	For the total patient sample (mild-to-severe headaches), 2-h pain-free rates were significantly higher than placebo (22%) on both eletriptan 20 mg (35%; P < 0.01) and eletriptan 40 mg (47%; P < 0.0001). For the cohort of patients who treated their headache when the pain intensity was mild, the 2-h pain-free rate on eletriptan 40 mg was 68% compared with 25% on placebo (P < 0.0001).
Brandes et al.[20]	Adults – Sum+Naproxen= 40.3 (SD 11) / Sum= 40.1 (SD 10.9) / Naproxen=39.4 (SD 11.3) / Plac =40 (SD 11.1) n=1,441 (187 male and 1,254 female)	Sumatriptan 85 mg + Naproxen Sodium 500 mg Sumatriptan 85 mg Naproxen sodium 500 mg Placebo Single tablet for treatment of a single migraine attack	Incidence of headache relief after 2 hours after dosing - Sum+Naprox - 65%, Sum - 55%, Naprox - 44%, Plac - 28%.
Brandes et al.[20]	Adults – Sum+Naproxen= 39.4 (SD 11.2) / Sum= 40.3 (SD 11.4) / Naproxen= 40.4 (SD 11.6) / Plac= 40.6 (SD 10.7) n=1,468 (151 male and 1,317 female)	Sumatriptan 85 mg + Naproxen Sodium 500 mg Sumatriptan 85 mg Naproxen sodium 500 mg Placebo Single tablet for treatment of a single migraine attack	Incidence of headache relief after 2 hours after dosing - Sum+Naprox - 57%, Sum - 50%, Naprox - 43%, Plac - 29%. Similar pattern of results was observed for absence of photophobia and absence of phonophobia. After imbalances in incidences of nausea, the incidence of absence of nausea 2 hours after dosing was significantly higher wih sum+naprox than with placebo. But not differ between sum+naprox and placebo in study 2.
Brandes et al.[71]	Adults – Frovatriptan 2.5 mg Q.D.=37.8 (±7.9) Frovatriptan 2.5 mg B.I.D.=38.9 (±7,6) Placebo=37.9 (±7.2) n=427 (all female)	Frovatriptan 2.5 mg QD Frovatriptan 2.5 mg BID Placebo Day 1 - q.d. group received 5 mg of active drug in the morning and placebo in the evening; the b.i.d. group received 5 mg frovatriptan in both the morning and evening; placebo group received two placebo tablets in the morning and evening. Thereafter, patients received placebo, frovatriptan 2.5 mg q.d., or frovatriptan 2.5 mg b.i.d. on days 2–6.	The mean number of headache-free PMPs (perimenstrual periods) per patient (primary endpoint) was significantly higher in the two frovatriptan groups [0.69 PMPs (q.d.) and 0.92 PMPs (b.i.d.) compared with placebo (0.42 PMPs) representing 64% (q.d.) and 119% (b.i.d.) increases in the mean number of headachefree PMPs per patient. Patients in the b.i.d. group experienced an increase in the mean number of headachefree days with each progressive PMP, increasing to 4.1 (1.7) in PMP 1, 4.5 (1.6) in PMP 2, and 4.7 days (1.4) in PMP 3. Over all PMPs, the mean (SD) number of headache-free days was 3.6 (1.4) for placebo vs. 4.0 (1.4) for the q.d. frovatriptan regimen and 4.2 (1.5) for the b.i.d. frovatriptan regimens (p<0.0001 frovatriptan q.d. or b.i.d. vs. placebo).
Bussone et al.[72]	Adults – 37±10.6 (18-65) years n=233 (male 49; female 184)	oral sumatriptan (50 mg) placebo (PLO) multiple attacks of migraine (a total of 12 migraine attacks, within each block of 4 attacks, three were treated with active medication and one with placebo)	In all attacks, the efficacy rate was statistically significant for sumatriptan versus placebo (PLO) in 2 or 4 hours (2 hours: sumatriptan 60%, PLO 38%, p<0.001; 4 hours sumatriptan 79%, PLO 47%, p <0.001). Oral sumatriptan was also effective in relieving associated symptoms and reducing clinical disability in most attacks. The reported adverse events were few, all of them of mild to moderate intensity and resolved spontaneously. The most frequently reported symptoms were gastrointestinal. Although the incidence of adverse events did not differ between treatment groups.
Cady et al.[21]	Adults – Sumatriptan 39.8 ± 9.6; Placebo -39.6 ± 9.7 n=574 (501 female and 73 male)	Sumatriptan 6 mg SC Placebo (0.5-mL subcutaneous injection over the deltoid muscle)	Pain relief and pain-free at 1h after treatment. Pain relief 1h - Sumatriptan 79% (515/734) vs Placebo 22% (81/370) (p<0.001). Pain-free 1h - Sumatriptan 49% (356/734) vs Placebo 9% (35/370) (p<0.001).
Cady et al.[21]	Adults – Sumatriptan 40 ± 9.8; Placebo 37.7 ± 10 n=530 (478 female and 52 male)	Sumatriptan 6 mg SC Placebo	Pain relief and pain-free at 1h after treament. Pain relief 2h - Sumatriptan 81% vs Placebo 34% (p<0.001). Related migraine sysptoms 1h - Photophobia - Sumatriptan - 43% vs Placebo 76% (p<0.001). Nausea - Sumatriptan 27% vs Placebo 51% (p<0.001).

Cady et al.[73]	Adults - mean age 41.2 and (range 18-76 years) n=100 (male 9 and female 91)	Sumatriptan 6 mg sc, Placebo Four headaches of moderate or severe intensity (grade 2 or 3) were treated in the clinic with a single dose of either 6 mg SC sumatriptan (three attacks) or placebo (one attack) in the upper arm or thigh	Sumatriptan statistically outperformed placebo on all efficacy measures, including pain severity; presence/absence of nausea, vomiting, phonophobia, and photophobia; rescue medication use; and clinical disability. Efficacy was consistently maintained with repeated administration. For all attacks, pain relief 90 minutes postdose occurred in 86% to 90% of sumatriptan-treated patients, compared with 9% to 38% of placebo-treated patients
Cady et al.[74]	Adults – mean: 41.5 years [frovatriptan-placebo: 40.4 years; placebo-frovatriptan: 42.5 years;] n=275 (36 males and 239 females)	Oral frovatriptan 2.5 mg Placebo The patients could take up to two doses of study medication per migraine attack.	When patients received frovatriptan as the first dose, it was more effective than placebo in terms of the proportion of patients who were pain free at 2 h (28% vs 20%, p=0.04). This benefit was sustained up to 4 h post-dose (p=0.003). Early use of frovatriptan significantly reduced re-medication (p<0.001). Twenty-four-hour headache recurrence was low in both early (4%) and later use (6%) groups. Sustained pain-free response occurred in 40% of frovatriptan early use patients compared with 31% of later use patients (p<0.05). Early use prevented headache progression: 69%-78% had mild/no headache 2-4 h after dose 1 frovatriptan compared with 54%-63% taking dose 1 placebo (p<0.001). Early use reduced pain burden and functional disability (p≤0.001). More patients rated early use of frovatriptan as excellent or good (57% vs 46%).
Cady et al.[75]	Adults – Rizatriptan - 40y; Placebo - 42 n=207 (187 female and 20 male)	Rizatriptan 10 mg ODT (orally disintegrating tablet) placebo	The percentage of participants reporting pain freedom at 2 hours after taking study drug was significantly greater for rizatriptan ODT (66%) compared with placebo. The percentage of participants reporting sustained pain freedom between 2 and 24 hours post-dose also was significantly greater for rizatriptan ODT (52%) compared with placebo. The proportion of participants reporting 2-hour pain freedom in the placebo groups was similar regardless of education.
Cady et al.[74]	Adults – 42.0(10.5) years n=212 (Male 35 and Female 177)	22 mg AVP-825 nasal spray (a drug–device combination of low-dose sumatriptan powder - 22 mg loaded dose) Placebo device	A significantly greater proportion of AVP-825 patients reported headache relief at 2 hours post-dose compared with those using the placebo device (68% vs 45%, p=0.002, odds ratio 2.53, 95% confidence interval [1.45, 4.42]). Between-group differences in headache relief were evident as early as 15 minutes, reached statistical significance at 30 minutes post-dose (42% vs 27%, p=0.03), and were sustained at 24 hours (44% vs 24%, p=0.002) and 48 hours (34% vs 20%, p=0.01. Patients treated with AVP-825 were pain-free (34%) at 2 hours compared with placebo device (17%; p=0.008). More AVP-825 patients reported meaningful pain relief (patient interpretation) of migraine within 2 hours of treatment vs placebo device (70% vs 45%, p<0.001), and fewer required rescue medication (37% vs 52%, p=0.02). Total migraine freedom (patients with no headache, nausea, phonophobia, photophobia, or vomiting) reached significance following treatment with AVP-825 at 1 hour (19% vs 9%; p=0.04). There were no serious adverse events (AEs), and no systemic AEs occurred in more than one patient.
Cady et al.[74]	Adults – 39,8 (SD 10,4) (Range from 19 to 61 years) n=20 (80% female and 20% male)	3 mg SC sumatriptan 6 mg SC sumatriptan to treat 1 attack	The primary efficacy endpoint was the proportion of subjects reporting freedom from pain at 60 min postdose. Pain-free 60 min postdose – 3 mg SC Sumatriptan - 50% vs 52.6% 6mg SC Sumatriptan (p=0.087). There was no difference in pain-free between treatments in 30, 60, 90 and 120 min postdose. Pain relief 60 minutes postdose – 3 mg SC Sumatriptan 83.3% vs 6 mg SC Sumatriptan 73.7% (p=0.48). As pain-free there were no difference between treatments at 30, 90 and 120 minutes post dose. No difference also, in patients experienced relief from nausea (p=0.91), photophobia (p=0.89), or phonophobia (p=0.88).
Carpay et al.[76]	Adults – 18-65 years n=124 (male 23 and female 101)	Group A: sumatriptan 0.5 ml of the 15 mg/ml subcutaneous first and oral sumatriptan 100 mg during the second period Group B: the order was reversed	Efficacy was evaluated 2 h after the administration of subcutaneous and 4 h after the administration of oral sumatriptan. Subcutaneous sumatriptan was significantly more effective than oral sumatriptan in relieving headache (over all 3 attacks 78% vs 61% improvement), improving clinical disability (55% vs 41% improvement) and relieving nausea (69% vs 53%), vomiting (72% vs 32%) and phono or photophobia (67% vs 49%). Median time to recurrence was shorter after subcutaneous (12.5 h) than after oral sumatriptan (18 h); the number of patients experiencing a recurrence was similar. Patients reported more adverse events after subcutaneous sumatriptan (1.32 per attack) than after the oral form (0.85 per attack), but all adverse events were mild to moderate in intensity and of short duration.
Carpay et al.[77]	Adults – Sumatriptan 50 mg tablet = 41.5 (SD 11.9) Sumatriptan 100mg tablet = 39.7 (SD10.9) Placebo = 40.6 (SD 10.3) n=432 (358 female and 74 male)	Sumatriptan 100 mg and 50 mg tablets Placebo single migraine attack	Sumatriptan tablets 50 mg and 100 mg were significantly more effective than placebo in conferring freedom from pain 2 hours after dosing (primary end point). In the intent-to-treat population, 66.2% of patients who received sumatriptan 100 mg and 51.1% of patients who received sumatriptan 50 mg were pain free 2 hours after dosing, compared with 19.6% of those who received placebo.

Charlesworth et al.[78]	Adults - Men and women 18–65 years. n=1458 (female 1343 and male 115)	Zolmitriptan nasal spray (5.0, 2.5, 1.0, 0.5 mg), Zolmitriptan oral tablets 2.5 mg Placebo treatment of three separate moderate or severe migraine headaches	Each dose of zolmitriptan nasal spray produced a greater 2-hour headache response rate than placebo (70.3%, 58.6%, 54.8% and 41.5% for zolmitriptan nasal spray 5.0, 2.5, 1.0 and 0.5 mg, compared with 30.6% for placebo [all p<0.001 vs placebo]). The 2-hour headache response rate for zolmitriptan nasal spray 5.0mg was significantly higher than that of the zolmitriptan 2.5mg oral tablet (61.3%; p<0.05), while comparisons of nasal spray 0.5, 1.0 and 2.5 mg with zolmitriptan 2.5 mg oral tablet were not statistically significant. The nasal spray 5.0 and 2.5 mg showed a rapid onset of action, with a significant difference in headache response compared with placebo from 15 minutes through 4 hours after administration and a significant difference between the nasal spray 5.0mg and 2.5 mg oral tablet from 15 minutes through to 2 hours (the other nasal spray doses were not statistically significant compared with 2.5 mg oral tablet). Zolmitriptan nasal spray resulted in pain-free rates that were dose dependent. While all doses from 1.0mg upwards produced significant pain-free outcomes from 30 minutes versus placebo, only the 5.0 mg dose produced pain-free rates significantly superior to both placebo and the 2.5 mg oral tablet
Christie et al.[79]	Adults - mean age 37.3 years (18-70) n=439 (16,6% male and 83.4% female)	Rizatriptan 10 mg tablet Ergotamine 2 mg + caffeine 200 mg tablet a single migraine attack	There are 2 co-primary efficacy analysis: 1. preference for one medication over the other and 2. pain free at 2 h. Pain free 2 h - 49% rizatriptan vs 24.3% ergotamine/caffeine. Medication preference – 69.9% (223) rizatriptan vs 30.1% (96) ergotamine/caffeine, 39 patients (10.9%) did not express a preference for one of the two treatments. The hazard ratio respect to time to headache relief was 2.05 (95% CI 1.72, 2.44). This means that at any time in the 2-hour period, headache in a patient on rizatriptan was more than twice as likely to be relieved within the next few minutes than in a patient taking ergotamine/caffeine.
Colman et al.[80]	Adults – Almotriptan: 41.25±10.09 (18 to 71) years; Sumatriptan: 40.26 ± 10.08 (18-65) years. n=1,173 (1044 female and 129 male)	Almotriptan 12.5 mg capsule Sumatriptan 50 mg capsule The first dose of study medication was taken at the onset of a moderate or severe migraine. The second dose was taking if patient experienced a relapse (an increase in pain severity to moderate or severe within 24 hours after the initial dose, for those responding to the initial dose)	A total of 1,173 patients were treated with almotriptan or sumatriptan. There were no significant differences between the 2 treatment groups in terms of satisfaction with pain relief; however, patients in the almotriptan group were significantly more satisfied (less bothered) with side effects than those receiving sumatriptan (p=0.016).
Connor et al.[81]	Adults – Telcagepant 280 mg/300 mg - 42.5±10.9 years; Rizatriptan 10 mg - 41.9±11.1 years. n=954 (739 female and 215 male)	Telcagepant 280/300 mg Rizatriptan 10 mg	Both telcagepant and rizatriptan were generally well tolerated. The overall incidence of clinical adverse events was similar between the treatment groups. Rizatriptan appeared numerically more effective than telcagepant for treating mild, moderate, or severe migraine attacks at 2 hours post dose. At 24 hours post dose, telcagepant showed higher responder rates for absence of phonophobia and nausea, and comparable rates for 2 to 24-hour sustained pain freedom and photophobia. Both telcagepant and rizatriptan demonstrated a consistent treatment effect over time, without evidence to suggest the development of tolerance.
Cull, Price, Dunbar[82]	Adults – Group A - 41±10.8; Group B - 40.5±10.3 years. n=881 (155 male 726 female)	Dose 1 - Sumatriptan 6 mg sc – both group at the onset of a migraine headache of moderate or severe intensity Dose 2 (headache recurrence only): Group A Sumatriptan 6 mg SC Goup B Placebo	At each attack, 6 mg sumatriptan given subcutaneously was significantly (p<0.0005) more effective than placebo at relieving recurrent headache after one hour; 83% of patients reported headache relief one hour after the initial dose of sumatriptan. Sumatriptan was generally well tolerated.
Dahlöf, Edwards, Tolth[83]	Adults – 45 ± 11 years n=27 (22 female 5 male)	Sumatriptan SC 8 mg Placebo (saline) 0.5 ml One migraine attack	Primary outcome measure was the number of patients who obtained complete or almost complete headache relief within 30, 60, 90, 120 min of taking study medication. Headache relief at 60 min - Sumatriptan 84% vs Placebo 11% (p<0.001); 90 min - Sumatriptan 73% vs Placebo 7% (p < 0.001); 120 min Sumatriptan 63% vs Placebo 0. Sumatriptan was significantly more effective than placebo in relieving nausea and photophobia. Before treatment 95% of patients had this symptom. After 120 minutes – Sumatriptan – 16% vs Placebo 79%. Rescue medication at 120 min – taken by 89% from placebo vs 11% from sumatriptan group (p<0.001).
Dasbach et al.[84]	Adults – mean age 40,6 years n=407 (84% female and 66 16% male)	Rizatriptan 10 mg Placebo 3 migraine attacks with rizatriptan and 1 with placebo	Hours of work loss due to absenteeism - Placebo – 2.2h/ Rizatriptan – 0.7h. Period working with symptoms - Placebo - 4,7h/ Rizatriptan - 4,2h Effectiveness on the job - Patients taking rizatriptan was 4,5% greater in comparison with placebo. Rizatriptan decreased the total number of hours of work loss by 1.1h per migraine attack treated compared with placebo.

Diamond et al.[85]	Adults - mean of 40 years of age. n=1086 (956 females and 130 males)	Sumatriptan nasal spray (5, 10, or 20 mg) Placebo up to 3 migraine attacks. Administered via a 1-shot nasal applicator into either nostril	Across attacks, headache relief in the 20, 10, and 5 mg drug and placebo groups was experienced 120 minutes postdose by 60%, 54%, 44%, and 32% of patients, respectively (p<0.05 for each sumatriptan nasal spray group vs placebo, for the 10-mg vs 5-mg drug group, and for the 20-mg vs 5-mg drug group). Two thirds of the 20 mg patients treating 3 attacks experienced relief at 2 hours postdose for at least 2 of 3 attacks. Clinical disability scores at 120 minutes in the 20, 10, and 5mg drug and placebo groups reflected no or mild impairment in 70%, 67%, 57%, and 50% of patients, respectively (p<0.05 for the 10 or 20 mg drug group vs placebo group, and for the 20-mg vs 5-mg drug group). Similar efficacy rates were observed for nausea, photophobia, and phonophobia. The incidence of adverse events was not dose related. The most frequently reported adverse event in the active treatment groups was taste disturbance (bad, bitter, or unpleasant).
Dib et al.[86]	Adults – 38.1±11.4 years n=235 (female 83.4% female and 16.6% male)	Ketoprofen 75 mg; Ketoprofen 150 mg; Zolmitriptan 2.5 mg Placebo; (comparisons between all treatments) four consecutive attacks with severe or moderate headache Each treatment was enclosed in opaque soft gelatin capsules	Results are based on 838 attacks with a severe or moderate headache that were evaluable at 2 hours. Relief was reported for 62.6% of headaches treated with ketoprofen 75 mg, 61.6% with ketoprofen 150 mg, and 66.8% with zolmitriptan. The difference between the three active treatments and placebo (27.8% relief) was highly significant. Headaches at 2 hours disappeared more frequently for the active treatments than for placebo.
Diener[87]	Adults – L-ASA = 41.5y (SD: 11.8); Sumatriptan = 40.9y (SD 11); Placebo = 39,8y (SD 11.7) 276 (55 male and 221 female)	Lysine acetylsacicylate iv 1.8 g Sumatriptan sc 6 mg Placebo One administration	The main result of this study was the significant difference (p=0.001) in efficacy, expressed as headache relief from grade 3 or 2 to grade 1 or 0, within 2 hours after administration of L-ASA and sumatriptan compared to placebo. Placebo was significantly inferior to both verum drugs (p<0.0001). Sumatriptan achieves a higher rate of headache-free patients after 2h, however was associated with a significantly higher incidence of adverse events.
Diener et al.[88]	Adults - ranged from 18 to 64 years (median age 41 years) n=924 (781 females and 143 males)	Alniditan (1.4 mg and 1.8 mg) sc Sumatriptan (6 mg) sc Placebo one single treatment.	The number of subjects who were pain free at 2 h (primary endpoint) was: 22 (14.1%) with placebo, 174 (56.3%) with alniditan 1.4 mg, 87 (61.7%) with alnditan 1.8 mg and 209 (65.9%) with sumatriptan 6 mg. Alniditan 1.4 mg was significantly better (P < 0.001) than placebo and sumatriptan was significantly better (P = 0.015) than alniditan 1.4 mg. The number of responders (reduction of headache severity from moderate or severe headache before treatment to mild or absent at 2 h), was 59 (37.8%) on placebo, 250 (80.9%) on alniditan 1.4 mg, 120 (85.1%) on alniditan 1.8 mg, and 276 (87.1%) on sumatriptan. Recurrence rates were: 22 (37.3%) with placebo, 87 (34.8%) with alniditan 1.4 mg, 35 (29.2%) with alniditan 1.8 mg and 108 (39.1%) with sumatriptan. Adverse events occurred in 577/924 (62.4%) subjects, 39.5% with placebo, 69.3% with alniditan 1.4 mg, 64.5% with alniditan 1.8 mg and 66.2% with sumatriptan 6 mg.
Diener et al.[89]	Adults – Eletriptan 80 mg - 40 ± 11; Eletriptan 40 mg - 40 ± 11; Cafergot 40 ± 10; Placebo 42 ± 11 n=733 (640 female and 93 male)	Eletriptan 80 and 40 mg Cafergot (ergotamine tartrate 2 mg, caffeine 200 mg) Placebo tablets	The primary efficacy endpoint was headache response (improvement from severe or moderate to mild or no pain) at 2 h - Eletriptan 80 mg 68%, Eletriptan 40 mg 54%, Cafergot 33% and Placebo 21% (p<0.01 for all comparisons). Secondary efficacy measures: pain-free rates at 2 h - Eletriptan 80mg 38%, eletriptan 40mg 28%, Cafergot - 10%, Placebo - 5%.
Diener et al.[30]	Adults – Acetylsalicylic acid 38.8, Ibuprofen 38.4, Sumatriptan 38.2 and Placebo 38.3 years. n=313	effervescent acetylsalicylic acid (ASA) 500 mg capsule Ibuprofen 400 mg gelatin capsules containing sumatriptan tablets 50 mg Placebo Single dose	The percentage of patients with reduction in headache severity from moderate or severe to mild or no pain (primary endpoint) was 52.5% for ASA, 60.2% for ibuprofen, 55.8% for sumatriptan and 30.6% for placebo. All active treatments were superior to placebo (P<0.0001), whereas active treatments were not statistically different. The number of patients pain-free at 2 h was 27.1%, 33.2%, 37.1% and 12.6% for those treated with ASA, ibuprofen, sumatriptan or placebo, respectively. The difference between ASA and sumatriptan was statistically significant (p=0.025).
Diener[90]	Adults – Almotriptan 12.5mg – 41.1 (SD 11.4); Placebo – 41.4 (SD 12) years n=221 (192 female and 29 male)	Almotriptan 12,5mg Placebo tablets	Efficacy measure was pain relief at 2 h after administration of study medication. An additional endpoint assessed here is complete relief. Pain relief 2h for patients with a severe baseline pain intensity - Almotriptan 46,4% vs Placebo - 25% (p<0.05). Pain relief 2h for patients with a moderate baseline pain intensity - Almotriptan 50% vs Placebo 15% (p<0.05). Complete pain relief 2h - Almotriptan 17,1% vs Placebo 4,4%; (p<0.05).

Diener et al.[91]	Adults – sumatriptan: 41.1 (14.2), Almotriptan 41.1 (11.4), placebo 41.4 (12.0) n=221 (male 29 and female 192)	Almotriptan 12.5 mg Placebo Tablets	In the first attack, 221 of 302 participants (73%) did not achieve 2-hour pain relief with sumatriptan and were randomized to treatment of their second attack with almotriptan 12.5 mg or placebo. Of the 198 sumatriptan nonresponders who treated their second attack (99 almotriptan; 99 placebo), 70% had severe headache pain at baseline. Two-hour pain-relief rates were significantly higher with almotriptan compared to placebo (47.5% vs 23.2%; p<0.001). A significant treatment effect for almotriptan was also seen in pain-free rates at 2 hours (33.3% vs 14.1%; P < .005) and sustained freedom from pain (20.9% vs 9.0%; p<0.05). In the second attack, 7.1% of patients in the almotriptan group experienced adverse events compared to 5.1% in the placebo group (P = .77).
Diez, Straube, Zanchin[92]	Adults – 36.3 (10.4) years n=372 (Female: 319 and Male: 53)	Rizatriptan 10 mg followed by almotriptan 12.5 mg, and reverse sequence tablets for the acute treatment of two migraine attacks	Almotriptan was preferred by 55% of patients but the difference was not statistically significant. Efficacy was the principal determinant of patient preference for one or the other triptan, but a significantly greater proportion of patients preferring almotriptan did so because they experienced fewer AEs associated with treatment. The two treatments were of comparable efficacy in measures of pain relief (74% versus 76%, almotriptan versus rizatriptan) and both treatments were safe and well tolerated
Djupesland, Docekal[93]	Adults – 42 years [sumatriptan 10 mg - 40.6 (21.0–59.0) years; sumatriptan 20 mg - 42.7 (18.0–58.0) years; placebo - 42.8 (21.0–64.0) years;] n=117 (100 females and 17 males)	Sumatriptan 10 mg or 20 mg Placebo single treatment day Nose powdered drug device with nosepiece	A greater proportion of subjects who received sumatriptan were pain-free at 120 minutes compared with those who received placebo (10 mg/20 mg sumatriptan vs. placebo 54% / 57% vs. 25%, p<0.05). Significant benefits were also observed for pain relief at 120 minutes (84% / 80% vs. 44%, P<0.001/.01) and as early as 60 minutes (73% / 74% vs. 38%, P<0.01) and for 48 hours sustained pain-free (P<0.05). Treatment-related adverse events were rare, with a metallic taste being the most commonly reported (10% / 13%).
Dodick et al.[94]	Adults – Zolmitriptan 5mg nasal spray - 40.7 ± 10.4 years; Placebo - 40.7 ± 10.3 years n=1868 (1,620 female and 248 male)	Zolmitriptan 5mg nasal spray Placebo Treat up to two migraine attacks, each with a single dose of study medication	The headache response rate at 2 hours post-dose was 66.2% for the zolmitriptan group, compared with 35.0% for the placebo group (p<0.001). Zolmitriptan nasal spray also produced significantly higher headache response rates than placebo at all earlier timepoints assessed, starting as early as 15 minutes post-dose (p<0.001). Similar results were obtained for the analysis of the first attack. Significantly higher pain-free rates were obtained with zolmitriptan nasal spray, compared with placebo, from 15 minutes post-dose onward (p<0.005). Zolmitriptan nasal spray was also significantly superior to placebo for headache response at 4 hours, sustained headache response at 24 hours and sustained pain-free rate at 24 hours. Zolmitriptan nasal spray was well tolerated, with most adverse events being of short duration and mild or moderate intensity.
Dowson et al.[95]	Adults range: 17 and 66 years; Almotriptan 12.5 mg - 42.8±10.7; Almotriptan 25 mg - 41.4±11.0; Sumatriptan 100 mg - 42.0±10.5; placebo - 40.2±10.1. n=668 (101 male and 567 female)	Oral almotriptan (12.5 mg and 25 mg) Sumatriptan (100 mg) Placebo single oral dose (capsules)	The primary efficacy assessment was migraine pain relief, improvement from severe or moderate pain to mild or no pain, at 2 h after treatment. Response rates, stratified for variation in baseline pain levels, for both almotriptan doses were equivalent to sumatriptan and significantly better than placebo. Other efficacy assessments confirmed the equivalence of the almotriptan groups with the sumatriptan group. Almotriptan 12.5 mg was as well tolerated as placebo (P=0.493) and significantly better tolerated than sumatriptan (P<0.001), in terms of the overall incidence of adverse events. There was no statistically significant difference in the incidence of adverse events between almotriptan 25 mg and sumatriptan 100 mg (P=0.376).
Dowson et al.[96]	Adults – Placebo: 206 female and 33 male; 204 female and 27 male; n=470 (410 female and 60 male)	Zolmitriptan 2.5 mg (orally disintegrating tablets) Placebo Acute treatment of a single moderate or severe migraine headache	Headache relief following zolmitriptan 2.5mg (63%) was significantly greater than with placebo (22%) at 2h post-dose (primary endpoint; p<0.0001). The zolmitriptan orally disintegrating tablet was also significantly more effective than placebo for 1, 2 and 4h pain-free response (8% vs. 3%, P=0.0207, 27% vs. 7%, p<0.0001, and 37% vs. 11%, p<0.0001, respectively). Of those patients stating a preference, 70% of patients preferred the orally disintegrating tablet to a conventional tablet.
Dowson, Massiou, Aurora[97]	Adults – Group 1 - 37 (19-49); Group 2 - 40 (19-50) n=115 (female only)	Sumatriptan 100 mg oral Placebo Four menstrual periods.	The primary study efficacy endpoints were the proportions of patients who reported headache relief at 4h post treatment. A small number of patients had mentrually related migraine, but efficacy analyses were conducted for the whole study sample. Headache relief at 4h - Patients inside menstrual window - Sumatriptan 67% vs Placebo 33% (p=0.0072) Outside menstrual window - Sumatriptan 79% vs Placebo 31% (p=0.0001). Complete headache relief at 4h - Inside menstrual window - Sumatriptan 49% vs Placebo - 10% (p=0.0001). Outside menstrual window - Sumatriptan 60% vs Placebo 9% (p=0.0001)

Evers et al.[48]	Adolescents – 13.9 ± 2.8 years n=32 (18 female and 14 male)	Oral zolmitriptan 2.5mg Ibuprofen 200 or 400 mg (according to child age) Placebo Three migraine attacks	The number of patients with pain relief after 2 hours was chosen as the primary outcome measure. Pain relief 2h - Zolmitriptan 62% vs Placebo - 28% (p<0.05) and Ibuprofen 69% (in comparison with placebo p<0.05). Pain free 2h - Zolmitriptan 45% vs Placebo - 7% (p<0,01) and Ibuprofen 48% (in comparison with placebo p<0.01). Sustained pain-free - Zolmitriptan 34% vs Placebo - 7% (p<0.05) and Ibuprofen 38% (in comparison with placebo p<0.05)
Facchinetti et al.[98]	Adults - mean age 37.5 n=226 (female only)	Sumatriptan 6 mg Placebo Pre-filled syringe in subcutaneous injection	The efficacy results were consistent for attacks one and two: 2 h after treatment in attacks one and two, 53 (73%) and 51 (81%;) of the sumatriptan-treated subjects, respectively, reported headache relief (reduction of a severe or moderately severe headache to a mild or no headache), compared with 27 (31%) and 18 (29%) of the placebo-treated subjects (p<0.001). Within 24 hours of treatment in attack one, 28 (53%) and 14 (52%) of the initial responders to sumatriptan and placebo, respectively, experienced headache recurrence.
Färkkilä et al.[99]	Adults – Eletriptan 80mg – 40.9 ± 10.2; Eletriptan 40mg – 41.4 ± 10.6; Placebo – 40.9 ±12 n=446 (385 female and 61 male)	Eletriptan 40 (E40) and 80 mg (E80) Placebo Oral tablets	The primary efficacy endpoint was 2h headache response after first attack. 2h headache response - E80 70% (106/152), E40 59% (91/154), Placebo 30% (22/74); E80 and E40 were significantly superior to placebo (p<0.0001) and E80 was significantly supererior to E40 (p<0.05). 2h pain free-response - E80 42% (64/152), E40 35% (54/154), Placebo 7% (5/74). Both doses are superior to placebo (p<0.0001). Sustained response - E80 45% (56/124), E40 39% (55/140), placebo 14% (10;74), both doses are superior to placebo (p<0,0005). Consistently response - The percentage of subjects who reported a response in 2 out of 3 headaches was significantly higher on E40 (66% - 74/112) and E80 (72% - 72/100) compared with placebo (15% - 5/34) (p<0.001).
Fernandes et al.[39]	Adults - Dipyrone – male 32.2 (DP 12.6) female 34.3 (DP 9.6); Metoclopramide – male 29 (DP 8.6) female 35.8 (DP 6.4) years. n=27 (14 male and 13 female)	Dipyrone IV Metoclopramide IV One migraine attack	Among male patients, it was observed that the percentage variation in pain scores before and after treatment was, in general, greater in patients treated with metoclopramide than in patients treated with dipyrone (p=0.052). No difference was seen between female patients (p=0.748).
Ferrari et al.[100]	Adults – Sum100 mg+Sum100 mg – 40.5 ±10.5 Sum100 mg+Placebo – 40.5 ± 10.5 n=1246 (1021 female and 225 male)	Sumatriptan 100 mg Placebo Tablets to treat up to three migraine attacks	The primary objective of the study was to compare headache improvement from moderate or severe at time 0 to none or mild at 4 h on sumatriptan 100 mg + sumatriptan 100mg and 100 mg + placebo. Headache improvement - 2 h after the first dose of 100 mg sumatriptan - 56% Sum+Sum vs 55% Sum+Plac. Headache improvement at 4 h - 77% Sum+Sum vs 80% Sum+Plac. Headache recurrence - 25% Sum+Plac vs 22% Sum+Sum
Freitag et al.[101]	Adults – Isometheptene Combination- 40.9 ± 9.6 Sumatriptan succinate – 43.3 ± 9.6 n=126 (112 female and 14 male)	Isometheptene Combination (65 mg isometheptene, 100 mg dichloralphenazone, and 325 mg acetaminophen) - 5 capsules taken over several hours Sumatriptan Succinate 25 mg (2 doses) capsules Placebo Single migraine attack	Primary outcome: % of patients with mild or no headache at 2 hours and/or 4 hours after the first dose of study medication, and % of patients who did not suffer a recurrence of headache within 24 hours of the initial dose. No or mild headache at 4 hours - Isometheptene combination 76% vs Sumatriptan 80% (X2 = 0.22). Patients without headache or had only a mild migraine at 24 hours - 82% in both groups.
Freitag et al.[102]	Adults – Rizatriptan 10 mg - 40 years; Placebo - 41 years n=277 (249 female and 28 male)	Rizatriptan 10 mg ODT Placebo Single migraine attack	There was a greater percentage of patients with elimination of nausea at 2 hours (primary efficacy endpoint) in the rizatriptan ODT group compared with the placebo group (70.3% vs 62.0%), P = 0.165, odds ratio (95% CI) = 1.45 (0.86, 2.46) - not statistically significant. There was a significantly greater percentage of patients who achieved 2-hour pain relief (secondary efficacy endpoint) with rizatriptan ODT compared with placebo (69.7% vs 54.3%), P = .012, odds ratio (95% CI) = 1.94 (1.16, 3.25).

Freitag et al.[103]	Adults – 40.4(10.8) n=315 (274 female and 41 male)	Almotriptan 12.5mg Placebo 3 consecutive migraine attacks Pharmaceutical form not informed	Attack 1: 2 h posttreatment 54.4%, 32.5%, 13.1%, and 0% of almotriptan-treated patients reported normal function, disturbed function, bed rest required, and ER/hospitalization respectively, compared with 38.1%, 45.2%, 16.1%, and 0.6% of placebo-treated patients. The differences in level of functional disability between the 2 treatment groups were statistically significant at 2 hours (P =0.007; Cochran-Mantel-Haenszel, stratified by center) and at 4 hours (P <0.001). Resolution of pain was associated with a normal level of function; at 2 hours posttreatment, 91.7% of patients in the total population who achieved pain-free reported normal function compared with 44.8%, 8.0%, and 0% of patients with mild, moderate, and severe pain, respectively. The absence compared with the presence of photophobia, phonophobia, and nausea at 2 hours also was associated with less disability (P < 0.0001 for each symptom). Treatment with almotriptan compared with placebo resulted in consistently better 24-hour MQoL scores with significant results for all 3 migraine headache attacks in the social function and feelings/concern domains. A logistic regression model determined that pretreatment functional level (P = 0.0117), pretreatment pain intensity (P = 0.0089), and pretreatment MIDAS score (P = 0.0152) were significant covariates of the proportion of patients who achieved normal function at 2 hours posttreatment.
Freitag et al.[36]	Adults – RA – 41.5 years (SD 10.3); R – 44.3 years (SD 10.6); A - 42 years (SD 11.7); P – 45.3 years (SD 10.9) n=172 (151 female and 21 male)	Rizatriptan 10 mg + Acetaminophen 1000 mg (RA); Rizatriptan 10 mg (R); Acetaminophen 1000 mg (A); Placebo (P) Oral tablet formulations to treat a single attack of migraine	The primary efficacy endpoint was pain relief (Grade 0 or 1) at 2 h. Pain relief 2h - RA 90%, R 77%, A 70%, P 46%. RA was statistically superior to A and P. Pain-freedom 2h - RA 54%, R 40%, A 26%, and p 15%. RA was statistically superior to A and P. Pain relief sustained 24h - RA 62%, R 53%, A 42% and P 15%. RA was statistically superior to P only. RA was statistically superior to A for absence of phonophobia (85% vs 60%, P = .009) and statistically superior to P for absence of phonophobia (85% vs 67%, P = .039), absence of nausea (92% vs 72%, P = .021), and absence of functional disability (65% vs 41%, P = .024).
Friedman et al.[104]	Adults – 31 to 37 years Metoclopramide = 34 years (31-37); Sumatriptan = 34 years (31/37) n=78 (67 female and 11 male)	Metoclopramide 20 mg + diphenhydramine 25 mg administered IV Sumatriptan 6 mg sc Single attack of migraine	The primary outcome, a comparison of the change in NRS (numeral rating scale) scores between time 0 and 2 hours in each arm, demonstrated a clinically and statistically insignificant advantage for the metoclopramide arm: 1.0. The secondary outcome, a comparison of the change in NRS (numeral rating scale) score between time 0 and 24 hours, revealed a clinically and statistically insignificant advantage for the metoclopramide arm: 1.1. At 2 hours - 59% of metoclopramide subjects and 35% of sumatriptan subjects were pain-free.
Friedman et al.[105]	Adults – TMB/DPH 34 (9.7) and Sumatriptan 32 (8.9) years n=40 (37 female and 3 male)	Trimethobenzamide 200 g + diphenhydramine 25 mg (TMB/DPH) as a single intramuscular injection Sumatriptan 6mg SC	By 2 hours sumatriptan subjects had improved by a mean of 6.1 and the TMB/DPH subjects had improved by a mean of 4.4 (95% CI for difference of 1.7: –0.1 to 3.4). By 24 hours after medication administration, sumatriptan subjects had a mean improvement from baseline of 4.9 as compared to 5.3 for TMB (95% CI for difference of –0.4: –2.4 to 1.6). The need for rescue medication was comparable between the groups. No serious or frequent adverse effects were noted in either group
Friedman et al.[106]	Adults - 18 to 64 years n=166 (144 female and 22 male)	Oral Naproxen 500mg Oral Sumatriptan 100 mg Single attack migraine	Naproxen group improved by a mean of 4.3 NRS (numeral rating scale) points, whereas the sumatriptan group improved by 4.1 points (95% CI for difference of 0.2 points: 0.7 to 1.1 points). Findings were virtually identical among the migraine subset (4.3 versus 4.2 NRS points; 95% CI for difference of 0.1 points: 1.3 to 1.5 points). Would patients want to take the same medication the next time: 71% Naproxen (95% CI 62% to 80%) and 75% (95% CI 66% to 84%) of sumatriptan patients answered yes. Adverse effect profiles were also comparable
Friedman et al.[107]	Adults - 18 to 63 years n=35 (28 females and 7 males)	Maxillary intraoral chilling (MIC) 40 minutes of bilateral Sumatriptan 50 mg oral Sham (tongue) chilling	Significant mean headache relief was obtained by maxillary chilling and sumatriptan at all time intervals (1, 2, 4 and 24 hours), with poor relief obtained by placebo. Maxillary chilling was more effective than sumatriptan at all time intervals. Significant nausea relief was obtained by maxillary chilling and sumatriptan at posttreatment and 2 and 4 hours later. At 24 hours, some headache and nausea recurrence were noted with sumatriptan. The repeated-measures analysis of variance indicated that both treatments, drug (P = 0.024) and maxillary chilling (P = 0.001), reduced the headache compared to the control group.

Fujita et al.[49]	Children and adolescents: Sumatriptan 25 mg: 14.5 (2.18); Sumatriptan 50 mg: 14.1 (1.96) and Placebo: 13.9 (2.04) n=144 (female 84 and male 60)	Sumatriptan 25 and 50 mg oral Placebo Single migraine attack	Patients who report pain relief at 2h post-treatment for the primary endpoint was higher in the placebo group than in the pooled sumatriptan group (38.6% vs 31.1%, 95% CI: 23.02 to 8.04, p=0.345). Patients who reported pain relief at 4h post-dose was higher in the pooled sumatriptan group (63.5%) than in the placebo group (51.4%) but failed to achieve statistical significance (p=0.142). At 4h post-dose, percentages of patients who were pain free or had complete relief of photophobia or phonophobia were numerically higher in the sumatriptan pooled group compared to placebo.
Gallagher et al.[108]	Adults – zolmitriptan 2.5 mg 39.9 (10.0); 5 mg 40.2 (10.5); Sumatriptan 25 mg 39.6 (10.2); 50 mg 40.6 (10.2) years n=1212 (1062 female and 150 male)	Zolmitriptan 2.5 mg, 5mg tablet Sumatriptan 25 and 50 mg tablet Treat a first and second (recurrence a single migraine attack) migraine attack	A headache response at 2 hours was noted in 67.1% of patients taking zolmitriptan 2.5 mg, and 64.8% of those taking zolmitriptan 5 mg, versus 59.6% of patients taking sumatriptan 25 mg, and 63.8% of those taking sumatriptan 50 mg. At 2 and 4 hours, the differences between zolmitriptan 2.5 mg, and sumatriptan 25 mg, were statistically significant (odds ratio=1.49 and 1.67, respectively; both P<.001). Statistically significant differences between zolmitriptan 2.5 mg, and sumatriptan 50 mg, were seen at 2 and 4 hours post dose (odds ratio=1.21 and 1.23, respectively; both P<.05). At 1 hour post dose, the headache response rate for zolmitriptan 2.5 mg, was numerically higher than response rates for sumatriptan 25 mg and 50mg (odds ratio=1.16, odds ratio=1.06, though they failed to reach statistical significance; P=.061, P=.461 respectively). Differences between zolmitriptan 5 mg, and sumatriptan 25 mg, were statistically significant at 1, 2, and 4 hours (odds ratio=1.43, 1.46, and 1.78, respectively; all P<.001) and at 1 and 4 hours versus sumatriptan 50 mg (odds ratio=1.28, P=.002; odds ratio=1.29, P=.012, respectively). Although not statistically significant at 2 hours, more patients responded to zolmitriptan 5 mg, than to sumatriptan 50 mg (odds ratio=1.16, P=.064). Patients receiving zolmitriptan 2.5 mg or 5 mg, achieved more pain relief over 24 hours than patients receiving sumatriptan 25 mg (odds ratio=1.47, and 1.54 respectively, both P<.001) or sumatriptan, 50 mg (odds ratio=1.17, P=.021; odds ratio=1.22, P=0.005, respectively
Garcia-Ramos et al.[109]	Adults – Eletriptan – 36.3 ± 11.1; Naratriptan 37.5 ± 11; Placebo 36.4 ± 11.1 years n=483 (390 female and 93 male)	Eletriptan 40mg tablet Naratriptan 2.5mg capsule Placebo Single migraine attack	The primary efficacy endpoint for the study was headache response at 2 h after the first dose of study medication for the index attack. Headache response 2 h - eletriptan (56%) compared to naratriptan 42%, P < 0.01). Headache response at 1 h - Eletriptan - 34%, Natriptan - 25% and Placebo - 21% and 4 h Eletriptan - 80%, Naratriptan - 67%, Placebo - 44%. Eletriptan showed higher pain-free rates at both 2 and 4 h (35% and 56%) compared with both naratriptan (18%; P <0.001 and 41%, P <0.01) and placebo (19%, P <0.001; 24%, P <0.0001). Among patients who achieved a 2 h headache response, headache recurrence rates were consistently low for eletriptan (29%), naratriptan (26%), and placebo (28%).
Geraud et al.[110]	Adults – Zolmitriptan-38.3±10.4 years; Sumatriptan-38.0±10.6 years; Placebo-37.9±9.7 years. n=1058 (174 male; 884 female)	zolmitriptan 5 mg or sumatriptan 100 mg placebo a single oral dose	A reduction in headache pain from moderate/severe at baseline to mild or no pain 2 h after taking study medication with no moderate or severe recurrence within 24 h (Primary Endpoint) was reported by 39%, 38% and 32% of patients treated with zolmitriptan, sumatriptan and placebo, respectively, with no significant difference between treatment groups. In patients with moderate headache at baseline, complete response was significantly greater following zolmitriptan than after placebo (48% vs. 27%; P50.01); there was no significant difference between sumatriptan and placebo groups (40% vs. 27%). In patients with severe baseline headache (where a greater reduction in headache intensity is required for a headache response), there was no significant difference between any groups in complete headache response rates. Secondary objectives were to compare headache and pain-free response rates at 1, 2 and 4 h post-dose. In addition, other secondary objectives were to compare the proportion of patients whose migraine-associated symptoms were effectively treated, use of escape medication after 2 h, incidence of recurrence, meaningful migraine relief, time to meaningful migraine relief, and degree of activity impairment at 1, 2, 4 and 24 h. For these secondary endpoints, active treatment groups were significantly superior to placebo for: 1-, 2- and 4-h headache response (e.g. 2-h headache response rates: zolmitriptan 59%; sumatriptan 61%; placebo 44%; P=0.01 vs. placebo); pain-free response rates at 2 and 4 h; alleviation of nausea and vomiting; use of escape medication and restoration of normal activity. The incidence of adverse events was similar between zolmitriptan and sumatriptan groups but was slightly lower in the placebo group.

Geraud, Compagnon, Rossi[111]	Adults – 41.6±10.0 and 40.9±10.7 years n=666 (100 male and 566 female)	Zolmitriptan 2.5 mg oral Acetylsalicylic acid 900 mg + metoclopramide 10 mg oral First and second (recurrence a single migraine attack) migraine attack	The percentage of patients with a 2-hour headache response after the first dose (primary endpoint) was 33.4% with zolmitriptan and 32.9% with acetylsalicylic acid plus metoclopramide [odds ratio 1.06, 95% confidence interval (CI) 0.77–1.47; p = 0.7228]. For most secondary endpoints, the two treatments demonstrated comparable efficacy.
Ghaderibarmi, Tavakkoli, Rossi[112]	Adults – Sumatriptan - 36.17±7.57; Valproate - 38.61 ± 11.41 years n=37 (7 male and 30 female)	Sumatriptan 6mg SC Valproate 15 mg/Kg IV Single migraine attack	The outcomes including pain severity at 0.5, 1, 2, 4, 24, and 48 hours after injection (VAS score was used to migraine severity). Sumatriptan VAS Score (before treatment: 0.84): 0.5h - 0.01, 1h - 0.023, 2h - 0.3, 4h -0.99, 24h - 0.68, 48h - 0.46. Valproate VAS Score (before treatment: 8.31): 0.5h - 3.31, 1h - 2.26, 2h - 2.15, 4h - 2.10, 24h - 1.68, 48h - 1.31.
Gijsmant et al.[113]	Adults - mean age 39.2 years n=418 (Female: 361 and Male: 57)	Rizatriptan 2.5mg, 5 mg, 10 mg Placebo Sigle migraine attack	At the primary timepoint of 2 h after the initial dose, the proportion of patients reporting pain relief was 47.6% for rizatriptan 10 mg; 45.4% for rizatriptan 5 mg; 21.3% for rizatriptan 2.5 mg; and 17.9% for pacebo. Seventy percent of patients on rizatriptan 10 mg reported pain relief at 4 h.
Goadsby et al.[114]	Adults – 39 (SD 10) years n=61 (10 male and 51 female)	Oral Sumatriptan 100mg Placebo Single migraine attack	Positive result was defined as a reduction in headache grade from 3 or 2 to 0 or 1. Reduction headache grade - Sumatriptan 45/89 [51 %] vs Placebo 9/93 [10%]; p < 0.01, x2 test). Use of rescue medication at 2 h - Sumatriptan 88% vs Placebo 41% (p < 0.05). Of the 28 patients who were headache-free at 2 h after sumatriptan, 11 (39%) had a recurrence of headache within the next 24 h.
Goadsby et al.[115]	Adults – 40 years (18 to 64) [placebo: 41±10 (21–66) years; sumatriptan-100mg: 40±10 (18–68) years; eletriptan-20mg: 40±11 (18–68) years; eletriptan-40mg: 41±11 (19–71) years; eletriptan-80 mg: 40±11 years (18–67);] years. n=692 (568 females and 124 males)	Eletriptan (20 mg, 40 mg, or 80 mg) tablet Sumatriptan (100 mg) capsules Placebo Single migraine attack, a second double-blind dose of study medication could be administered	At the primary endpoint (2 hours after dosing), headache response rates were 24% (30/126) for placebo; 55% (63/115) for sumatriptan 100 mg; 54% (70/129) for eletriptan 20 mg; 65% (76/117) for eletriptan 40 mg; and 77% (91/118) for eletriptan 80 mg. There was a difference compared with placebo (p<0.001) for all doses of eletriptan, and at 2 hours there was a difference between sumatriptan 100 mg, and eletriptan 80 mg (p<0.001). Headache-free rates at 2 hours were superior to placebo (6%; p<0.001) for both the 80-mg dose of eletriptan (37%) and the 40-mg dose (29%), with the 80-mg dose also being superior to 100 mg of sumatriptan (23%; p<0.05). Eletriptan and sumatriptan were well tolerated, and the majority of adverse events were mild or moderate in intensity and transient.
Goadsby et al.[116]	Adults - Almotriptan 39 ±11 and Zolmitriptan 40 ± 11 years n=1062 (902 female and 160 male)	Almotriptan 12.5 mg oral Zolmitriptan 2.5 mg oral single migraine attack	The primary endpoint was sustained pain free plus no adverse events, other endpoints included pain relief and pain free at several time points, sustained pain free, headache recurrence, use of rescue medication, functional impairment, time lost because of migraine, treatment acceptability, and overall treatment satisfaction. 2-h pain relief: Almotriptan 65.4%; Zolmitriptan: 70.2 % (p = 0.094) Pain relief at 24 h: Almotriptan 82.9%; Zolmitriptan: 83.8 % (p = 0.699) 2 h pain free: Almotriptan 43.5%; Zolmitriptan: 48.3 % (p = 0.117).
Göbel et al.[117]	Adults – mean age 45 years n=253 (230 female and 23 male)	Naratriptan 2.5 mg tablet Sumatriptan 100 mg tablet single migraine attack	Of the 164 naratriptan-treated and 181 sumatriptan-treated patients experiencing headache relief after ≥1 attack, headache recurrence 4 to 24 hours after treatment was reported by 74 naratriptan-treated patients (45%) and 101 sumatriptan-treated patients (57%; not statistically significant). In a subset of patients experiencing headache relief after 2 attacks, headache recurrence 4 to 24 hours after initial dosing was reported by 55 naratriptan and 77 sumatriptan-treated patients (41% and 57%, respectively; P = 0.005). The overall incidence of adverse events was 22% after treatment with naratriptan and 33% after treatment with sumatriptan. This incidence did not increase after the use of the second dose of naratriptan (20%) or sumatriptan (31%).
Goldstein et al.[118]	Adults - mean age 40.2 years n=1,329 (1,167 female and male 162)	Rizatriptan 5 and 10mg oral Sumatriptan 25 and 50mg oral two migraine attacks	The outcomes were time to pain relief (comparison between drugs) and pain relief at 2 hours. Pain relief - HR rizatriptan 5mg vs sumatriptan25 mg = 1.16, suggesting that patients on rizatriptan 5mg are 16% more likely to achieve pain relief in comparison to patients on sumatriptan 25 mg. HR rizatriptan10mg vs sumatriptan 50mg = 1.14 suggesting that patients on rizatriptan10 mg are 14% more likely to achieve pain relief in compariton to patients on sumatriptan 50mg. Pain relief at 2h – Rizatriptan 5mg - 33%, Sumatriptan 25mg - 28%, Rizatriptan 10mg - 72%, Sumatriptan 50mg - 68%, Placebo -38%

Goldstein et al.[119]	Adults – mean age 38.1 years n=171 (136 female and 35 male)	AAC (acetaminophen 500 mg, aspirin 500 mg, caffeine 130 mg) Sumatriptan succinate 50mg (25 mg per tablet) Placebo All study medications were individually encapsulated in hard gelatin capsules	AAC group experienced significantly greater pain intensity reduction or pain relief than those taking S50 or placebo. Pain intensity reduction and pain relief score for Sumatriptan 50mg group were higher than placebo group, but not to a statistically significant degree. Reduction of headache pain intensity from moderate/severe to mild/none - Sumatriptan 50mg group was significantly superior to AAC (30 minutes postdose); AAC group was significantly greater than in the Sumatriptan 50mg group (2, 3 and 4 hours postdose). The response rate of AAC versus placebo was significant from 90 minutes. The rate of response in the Sumatriptan 50mg group was greater than that in the placebo group at all time points, but not to a statistically significant degree. Utilization of the rescue medication showed statistically significant difference between Sumatriptan 50mg group (11.9% subjects) versus the AAC group (1.5% of subjects), at 4 hours postdose.
Goldstein et al.[120]	Adults – Sumatriptan ITS - 40,7 (SD 11,2) Placebo - 41 (SD 11) years n=454 (386 female and 68 male)	Sumatriptan transdermal system 6.5 mg Placebo patch Dose timing began at patch activation. Patients remained on study until one migraine headache was treated with the study patch or 2 months following randomization, whichever occurred first	Significantly greater proportion of patients who received the sumatriptan transdermal system were headache pain-free 2 hours after patch activation compared with placebo (18% vs 9%, respectively; p=0.0092). The sumatriptan transdermal system was associated with a significantly higher percentage of patients reporting headache pain relief 2 hours postdose (52.9% vs 28.6%, respectively; P <0.0001).
Gross et al.[121]	Adults – Sumatriptan - 44 ± 10.2; Placebo - 43 ± 11.3 years n=86 (69 female and 17 male)	Sumatriptan 6 mg sc Placebo Single migraine attack	Primary efficacy was headache relief at 60 minutes after the first injection. Headache relief 1 hour post treatment - Sumatriptan 42/48 (88%) vs Placebo 2/18 (11%) (P <0.001). Rate treatment as good or excellent - Sumatriptan (47/60, 78%) vs Placebo (4/26, 15%). Second dose - Sumatriptan (17/ 20, 85%) to treat recurrence and Placebo (21/24, 88%) to treat an ongoing headache following an ineffective response to the first dose. Adverse events - Sumatriptan 55% (33/60) vs Placebo 15% (4/26).
Gruffydd-Jones et al.[121]	Adults – had been less than 50 years old. n=401 (329 female and 72 male)	Sumatriptan 100mg oral and Sumatriptan 6 mg subcutaneous Three migraine attacks	Over 70% of patients who treated attack 1 in both treatment periods of the crossover phase reported headache relief with each formulation at 4 h. Only 3% of patients failed to respond to at least one of the formulations at this time point. At the end of the crossover phase patient preference for the injection more than doubled from the pretreatment level in those patients who were previously naive to sumatriptan. During the optional phase of the study, 38% of patients chose to treat some attacks with oral and some with subcutaneous sumatriptan
Gruffyd-Jones et al.[122]	Adults – Zolmitriptan 5mg = 41.7 ± 10.6; Zolmitriptan 2,5mg = 42.1 ± 10.7; Sumatriptn 41.9 ± 10.7 years. n=1522 (1299 female and 223 male)	Zolmitriptan 5 and 2.5mg tablets Sumatriptan 50mg tablets Single migraine attack	There were 2 primary efficacy endpoints: headache response at 2 h after treatment and proportion of patients with a headache response at 2 h after the first dose of study medication across all attacks treated. Headache response at 2h: Zolmitriptan 5mg – 65.7% vs Zomitriptan 2,5mg – 62.9% vs Sumatriptan 50mg - 66,6% (there were no difference between response rates in all treated attacks with 3 study medications, there were no statistically difference post 1 or 4h). Proportion of patients with 2h response: Zolmitriptan 5mg – 44.4% patients had a response in >80% of attacks, Zolmitriptan 2.5mg - 38,6% patients had a response in >80% of attacks, Sumatriptan 50mg – 43.1% patients had a response in >80% of attacks (p=0.14 versus zolmitriptan 2.5 mg and p=0.55 versus zolmitriptan 5 mg).
Hämäläinen, Hoppu, Santavuori[50]	Adolescents - 12,3 (8,3 - 16,4) years n=23 [12 female (52%) and 11 male (48%)]	Sumatriptan 50 mg oral for a body surface area of 0.75 to 1.5 m2 Oral Sumatriptan 100 mg for a body surface area of > 1.5 m2 Placebo One migraine attack with sumatriptan and for one with a matching placebo in random order	The primary endpoint of clinical efficacy was reduction of pain intensity by at least 50% after 2 hours. At 2 hours, reduction of pain intensity by 50% - Sumatriptan 7/23 (30%) vs placebo 5/23 (22%) (difference 9%, 95% CI for difference -21 to 38%, p = ns). Headache-free - Sumatriptan 5/23 (22%) vs placebo 2/23 (9%) (difference 13%, 95% CI for difference -9 to 35%, p = ns).
Havanka et al.[123]	Adults – 18 to 65 years n=643 (566 female and 77 male)	Naratriptan tablets (1, 2.5, 5, 7.5, and 10 mg) Sumatriptan tablets (100 mg) Placebo Single oral dose for a single migraine attack	1 hour headache relief: Narat 1 mg (25/85); Narat 2.5 mg (30/87); Narat 5 mg (34/93); Narat 7.5 mg (43/93); Narat 10 mg (40/96); Sumat 100 mg (35/98); Plac (20/91). 2 hours headache relief: Narat 1 mg (58/85); Narat 2.5 mg (52/87); Narat 5 mg (54/93); Narat 7.5 mg (68/93); Narat 10 mg (69/96); Sumat 100 mg (60/98); Plac (31/91). 4 hours headache relief: Narat 1 mg (64/85); Narat 2.5 mg (63/87); Narat 5 mg (65/93); Narat 7.5 mg (80/93); Narat 10 mg (80/96); Sumat 100 mg (80/98); Plac (39/91).

Henry, d'Allens[124]	Adults – Mean age was Sumatriptan 44±1.7 and Placebo 42±1,6 years. n=76 (10 males and 66 females)	Sumatriptan 6mg SC Placebo Patients having inadequate relief were allowed to use a second injection of test medication 1 hour later and rescue treatment between 2 hours and 24 hours after the first dose.	Headache relief was achieved within 2 hours after Sumatriptan in 26 patients (70%) compared to 8 patients (21%) in the placebo group (p<0.0001). Of these patients, 19 (51%) and 3 (8%) were, respectively, pain free at this time. A second injection of Sumatriptan was used respectively by 13 (35%) and 22 (58%) patients (p<0,024).
Ho et al.[51]	Adolescents 6-17 years old and mean 13.0 (2.9) years. n=977 (female 550 and male 427)	Rizatriptan (5 mg for <40 kg, 10 mg for ≥ 40 kg) Placebo Patients with moderate/ severe pain (non-responders) proceeded to take study medication in Stage 2	A higher proportion of 12–17 year old on rizatriptan had pain freedom at 2 hours compared with those on placebo, 87/284 (30.6%) versus 63/286 (22.0%), odds ratio = 1.55 [95% CI: 1.06 to 2.26], p = 0.025. Adverse events within 14 days of dose in 12–17 year old were similar for rizatriptan and placebo. The pattern of findings was similar in 6–17 year old.
Ishkanian et al.[125]	Adults – sumatriptan 39.6±12.3 (18 -70) years; placebo 41.0±11.3 (18-60) years. n=215 (151 females and 64 males)	Sumatriptan 50 mg tablet Placebo Single migraine attack	Significantly more patients treated with sumatriptan 50 mg achieved a positive headache response at 2 and 4 hours after administration compared with those treated with placebo (69% vs 43% at 2 hours and 76% vs 49% at 4 hours, respectively; both, P < 0.001). Significantly more sumatriptan-treated patients were free from sinus pain compared with placebo recipients at 2 hours (63% vs 49% placebo, P = 0.049) and 4 hours (77% vs 55%, P = 0.001). All treatments were generally well tolerated. The most common drug-related AEs reported in the sumatriptan and placebo groups, respectively, were dizziness (5% vs < 1%), nausea (3% vs 2%). No patients experienced any serious adverse effects.
Jelinski et al.[126]	Adults – mean age of 40 years [(39.8±9.7 years sumatriptan 50 mg, 39.8±11.4 years sumatriptan 100 mg, 40.7±9.8 years placebo)] years n=361 (309 females and 52 males)	Sumatriptan 50 mg Sumatriptan 100 mg Placebo Single migraine attack	Two-hour pain free rates were 16%, 40%, and 50% in the placebo group, sumatriptan 50 mg group, and the sumatriptan 100 mg group respectively (p < 0.001, active treatment groups vs placebo). The percentage of subjects who sustained a pain-free response for both 50 mg and 100 mg sumatriptan groups (24% and 27%) was significantly higher than in the placebo group (6%). After 4 hours, 25% of the 50 mg sumatriptan group and 13% of the 100 mg sumatriptan group experienced worsening of their migraine pain, compared to 46% of placebo patients (both p<0.001).
Jensen et al.[127]	Adults – 43 years (range 20-65) n=138 (125 female and 13 male)	Sumatriptan 6 mg subcutaneous Placebo	Sumatriptan 6 mg sc was significantly better than placebo at 30, 60, 90 and 120 min after injection in relieving moderate or severe headache to mild or none as well as relieving any headache to none. At 60 min after injection, the treatment response rate was 61% for sumatriptan and 6% for placebo. During the following open-phase trial of four attacks treated with sumatriptan, treatment response rates were 68-74%. During the total of 538 attacks treated, 12 attempts at using the self-injector failed. In the double-blind and open phases, 81% and 90% of patients respectively found the device easy or very easy to use. Adverse effects were benign and short lasting, but led 7 patients to discontinue the study.
Kelly et al.[128]	Adults – mean age sumatriptan 32 and chlorpromazine 35 years n=43 (29 Female and 14 male)	Sumatriptan 6 mg IM Chlorpromazine IV 12.5 mg increments to a maximum of 37.5 mg	No difference in efficacy between the sumatriptan regimen and the chlorpromazine regimen was found. Adverse effects were mild and equally distributed between the groups.
Klapper, O'Connor[31]	Subjects age not mentioned. n=30	Rizatriptan 10 mg wafer sublingual Placebo Single migraine attack	The primary efficacy measure was pain relief in 1 hour. Pain relief in 1 hour – Rizatriptan 50% (8/16) vs Placebo 50% (7/14). The average time to onset of significant relief - Rizatriptan was 25 min vs. Placebo 27 min (t=1.25, NS).
Klapper et al.[129]	Adults – Zolmitriptan 2.5mg – 41.1 ± 11.3 years; Placebo - 42 ± 10.3 years n=280 (39 male and 241 female)	Zolmitriptan 2.5 mg oral Placebo Single migraine headache	Primary endopoint was pain-free rate (i.e. 'no pain') at 2 h after the first dose of zolmitriptan 2.5 mg or placebo. Pain-free at 2 h - Zolmitriptan 43.4% vs. Placebo 18.4%; odds ratio (OR) 3.28, 95% CI 1.90–5.66, P < 0.0001. Progressed to more severe intensity within 2 h after treatment -Zolmitriptan 53.7% vs. Placebo 70.4%, P < 0.01. At 2 h after dosing patients able to perform normal activities -Zolmitriptan 68.4% vs. Placebo 50.7%, P < 0.01.

Klassen et al.[130]	Adults – 40.2 years n=613 (533 female and 80 male)	Naratriptan tablets 2.5mg, 1 mg, 0.25 mg or 0.1 mg Placebo One moderate or severe migraine attack	Headache relief (moderate or severe pain at dosing reduced to mild or no pain) 4 hours postdose was reported in 60% of patients receiving naratriptan 2.5 mg compared with 50%, 35%, 32%, and 34% of patients receiving naratriptan 1 mg, 0.25 mg, 0.1 mg, and placebo, respectively (P<0.05 naratriptan 2.5 mg and 1 mg versus placebo, 1 mg versus 0.1 mg, and 2.5 mg versus 0.1 mg and 0.25 mg). Clinical disability 4 hours postdose was reported as mild or none for 70% of patients receiving naratriptan 2.5 mg compared with 63%, 47%, 48%, and 48% of patients receiving naratriptan 1 mg, 0.25 mg, 0.1 mg, or placebo, respectively (P<0.05 naratriptan 2.5 mg and 1 mg versus placebo, 1 mg versus 0.1 mg, and 2.5 mg versus 0.1 mg and 0.25 mg). Four-hour efficacy for absence of nausea, photophobia, and phonophobia was similar to efficacy for headache relief at each dose. The adverse event profile of each dose of naratriptan was similar to that of placebo. No clinically relevant change in any safety measure was reported.
Kolodny et al.[131]	Adults – mean age 40 years n=1,447 (1,244 female and 203 male)	Rizatriptan 5mg tablets Rizatriptan 10mg tablets Sumatriptan 25mg tablets Sumatriptan 50mg tablets Placebo Acute treatment of migraine, two-attack crossover study	The primary objective of the study was to compare rizatriptan 10 mg and sumatriptan 50 mg in terms of time-to-pain relief during the 2 h after taking study drug. Hazard ratio [rizatriptan 10 mg vs sumatriptan 50 mg] = 1.10 [95% confidence interval (CI) 0.96, 1.26; P = 0.161]. Hazard ratio [Rizatriptan 5 mg vs sumatriptan 25 mg] = 1.22 (95% CI 1.06, 1.41, P = 0.007). Pain-free rates at 2h - Rizatriptan 5mg 33,4% vs Sumatriptan 25mg 27,4% [OD=1,34 - 95%CI 1.05, 1.72 p=0,002] / Rizatriptan 10mg - 38% vs Sumatriptan 50mg 33,6% [OD=1.23 - 95%CI 0.99, 1.52, p=0,059].
Kostic et al.[132]	Adults – IV Prochlorperazine with diphenhydramine - 31 (SD - 10); SC Sumatriptan - 28 (SD - 6) years n=66 (42 female and 24 male)	Prochlorperazine 10 mg IV with diphenhydramine 12.5 mg Sumatriptan 6 mg SC Single migraine attack	The primary outcome measure was the mean change in pain intensity from baseline to 80 minutes. The mean decrease in pain intensity in the IV prochlorperazine with diphenhydramine group was 73 mm compared with 50 mm in the subcutaneous sumatriptan group.
Krymchantowski, Filho, Bigal[133]	Adults - mean age of 39.7 years n=32 (75% female and 25% male)	Rizatriptan 10 mg tablet plus trimebutine 200 mg capsule Rizatriptan 10 mg Placebo, Two consecutive moderate or severe attacks	At 1 h postdose, 30 (46.8%) of 64 attacks treated with the combination resolved completely, vs. eight (12.5%) of the rizatriptan-treated attacks, a difference of 34% (P < 0.01). At 2 h postdose, 47 (73.4%) attacks treated with the combination vs. 20 (31.2%) of those treated with rizatriptan alone resolved completely, a difference of 42% (95% confidence interval 26, 58, P < 0.001). Regarding nausea and photophobia, the combination was also associated with significantly better response
Krymchantowski et al.[40]	Adults – mean age 31 (aged 18 to 48) years n=30 (2 male and 28 female)	Lysine clonixinate (LC) 200 mg IV Dipyrone (metamizol) 1000 mg IV Single migraine attack	At 30 minutes, 0% of the dipyrone group 13% of the lysine clonixinate (LC) group were pain free (p=0.46). At 60 and 90 minutes, 2 (13%) and 5 (33%) patients from the dipyrone group and 11 (73%) and 13 (86.7%) patients from the LC group were pain free (p<0.001). At 60 minutes, significantly more patients from the LC group were nausea-free (p<0.001). Regarding photophobia, there were no differences between groups at 60 minutes (p=0.11). The use of rescue medication at 2 hours did not differ among groups (p=0.50). Pain in the site of the injection was reported by more patients of the LC group compared to the dipyrone group (p<0.0001).
Lainez et al.[134]	Adults – almotriptan: 33.15 years (±8.8 years); ergotamine+caffeine: 33.84 years (±10.1 years) n=229 (199 females and 30 males)	Almotriptan 12.5 mg Ergotamine 2 mg plus caffeine 200 mg Treatment of two migraine attacks	Treatment with almotriptan was associated with a significantly greater proportion of patients achieving 2h pain-free (20.9% vs. 13.7%; P<0.05) and 2h pain relief (57.7% vs. 44.5%; P<0.01) compared with ergotamine plus caffeine therapy; significant differences were not seen at 1h. Rates for sustained pain-free and sustained pain-free plus no adverse events (AEs) also were significantly greater after almotriptan treatment than after the use of ergotamine plus caffeine (P<0.05). Almotriptan was associated with a significantly lower rate of photophobia at 90 min (P<0.05), phonophobia at 60, 90, and 120 min (P<0.05 to <0.01), and nausea and vomiting at 90 and 120 min (P<0.01) compared with ergotamine plus caffeine. A significantly greater proportion of patients were more satisfied with almotriptan (55.7% and 64%, 1st and 2nd attacks, respectively) than with ergotamine plus caffeine (36% and 44.3%,1st and 2nd attacks, respectively) - (P<0.05). Sixteen patients reported adverse events during almotriptan treatment and 27 patients during the ergotamine plus caffeine therapy. Most adverse events were mild-to-moderate and did not result in treatment-related discontinuations.

Landy et al.[22]	Adults – 37 years (37.8±8.5 years sumatriptan 50 mg; 37.9±8.4 years sumatriptan 100 mg; 37.6 ±7.6 placebo) n=447 (403 females and 44 male)	Sumatriptan 50 mg tablets Sumatriptan 100 mg tablets Placebo Single migraine attack	Sumatriptan 50 mg and 100 mg tablets were significantly more effective than placebo at conferring pain-free response 2 h post-dose (p<0.001 each sumatriptan group vs. placebo). The onset of efficacy vs. placebo for pain-free response was observed by 1 h post-dose for sumatriptan 100 mg (p<0.05). Sustained freedom from pain from 2 through 24 h post-dose was reported by 30 and 35% of patients in the sumatriptan tablets 50mg and 100mg groups, respectively, compared with 8% of placebo-treated patients (p<0.001 each sumatriptan group vs. placebo). Both doses of sumatriptan were well tolerated. The adverse events were generally slightly higher in the sumatriptan groups than in the placebo groups.
Landy et al.[22]	Adults – mean age - 37 years - 35.5±7.8 years sumatriptan 50 mg; 37.3±8.7 years sumatriptan 100 mg; 36.9±7.6 placebo;) n=369 (349 female and 20 male)	Sumatriptan 50 mg tablets Sumatriptan 100 mg tablets Placebo Single migraine attack	Sumatriptan 50 mg and 100 mg tablets were significantly more effective than placebo at conferring pain-free response 2 h post-dose (p<0.001 each sumatriptan group vs. placebo). The onset of efficacy vs. placebo for pain-free response was observed by 1 h post-dose for sumatriptan 100 mg (p<0.05). Sumatriptan 50 mg and 100 mg tablets were 30 and 31% compared with 14% of placebo-treated patients (p<0.05 each sumatriptan group vs. placebo). Both doses of sumatriptan were well tolerated. The adverse events were generally slightly higher in the sumatriptan groups than in the placebo group.
Lewis et al.[135]	Adults – mean age: 14.2 years n=171 (98 female and 73 male)	Zolmitriptan 5 mg nasal spray Placebo Crossover study 2-attacks	The onset of significant pain relief was apparent 15 minutes after treatment with zolmitriptan nasal spray. At 1 hour after the dose, zolmitriptan nasal spray produced a higher headache response rate than did placebo (58.1% vs 43.3%). Zolmitriptan nasal spray was also significantly superior to placebo in improvement in pain intensity, pain-free rates, sustained resolution of headache, and resolution of associated migraine symptoms. Return to normal activities was also consistently faster with zolmitriptan nasal spray than with placebo, with less use of any escape medication. Treatment with zolmitriptan nasal spray was well tolerated.
Linder et al.[52]	Adolescents – Placebo - 14.4 (12-17) years; Almotriptan 6.25 mg - 14.4 (12-17) years; Almotriptan 12.5 mg - 14.2 (12-17) years; Almotriptan 25 mg - 14.4 (12-17) years. n=548 (227 male and 321 female)	Almotriptan 6.25 mg oral Almotriptan 12.5 mg oral Almotriptan 25 mg oral Placebo 1 dose of study medication	The 2-hour pain-relief rate was significantly higher with almotriptan 25 mg compared with placebo (66.7% vs 55.3%; P = .022). The incidence of nausea, photophobia, and phonophobia at 2 hours (adjusted for baseline pain intensity) for the almotriptan 25 mg and placebo groups was not significantly different. The 2-hour pain-relief rates (unadjusted) were significantly higher with almotriptan 6.25 mg (71.8%), 12.5 mg (72.9%), and 25 mg (66.7%) than with placebo (55.3%; P = .001, P <.001, and P = 0.028, respectively). Rates for sustained pain relief also were significantly greater with almotriptan 6.25 mg (67.2%), 12.5 mg (66.9%), and 25 mg (64.5%) than with placebo group (52.4%), P < 0.01 for the 6.25- and 12.5-mg doses and P < .05 for the 25-mg dose. Age group subanalysis demonstrated significantly greater 2-hour pain relief rates with all 3 doses of almotriptan compared with placebo for patients aged 15 to 17 years, a significantly lower incidence of photophobia and phonophobia at 2 hours with almotriptan 12.5 mg compared with placebo for patients aged 15 to 17 years, and a significantly lower incidence of photophobia with almotriptan 12.5 mg compared with placebo for those aged 12 to 14 years. Almotriptan treatment was well tolerated, with the most common adverse events nausea, dizziness, and somnolence.
Lines, Vandormael, Malbecq[136]	Adults - mean age 40 years n=872 (715 female and 157 male)	Oral rizatriptan 5 mg, Oral sumatriptan 50 mg Placebo Single migraine attack	Active drugs were superior to placebo at reducing headache pain and were similarly effective.
Lipton et al.[137]	Adults - (mean age, 38.1 years) n=249 (female 86% and male 14%)	Sumatriptan 50 mg tablets Placebo Series of 5 headaches	Sumatriptan was superior to placebo for headache response 4 hours postdose (primary endpoint) across all headache types (migraine 66% versus 48%; P<.001; migrainous 71% versus 39%; P<.01; tension-type 78% versus 50%, P<.001). Sumatriptan was also superior to placebo for pain-free response 4 hours postdose for migraine (41% versus 24%, P<.001) and tension-type headaches (56% versus 36%, P=.001). Sumatriptan provided superior pain-free response 2 hours postdose for migraine (18% versus 7%, P<.0001) and tension-type headache (28% versus 14%, P=.0005) compared with placebo.
Loder et al.[138]	Adults – mean age 37.3 years n=524 (429 female and 95 male)	Rizatriptan ODT 10 mg Sumatriptan 50 mg tablet Two migraine attacks	Percentage of patients who preferred rizatriptan ODT 10-mg (57%, n=213) was significantly greater than those who preferred sumatriptan 50-mg tablet (43%, n=161) (P.01). A significantly greater percentage of patients reported pain relief after taking rizatriptan ODT than sumatriptan at the 45- and 60-minute time points (38% versus 29% and 58% versus 49%, respectively) (P.01). In addition, a significantly greater percentage of patients taking rizatriptan ODT reported a pain-free status at the 60- and 120-minute time points (23% versus 17% [P.05] and 60% versus 52% [P.01], respectively).

Loder et al.[139]	Adults – mean: 37 years range: 18 to 55 years [zolmitriptan: 37.2±7.4 (18-55) years and placebo: 37.9±7.2 (19-51) years] n=510 (all female)	Zolmitriptan 2.5 mg oral Placebo in a series of 5 headaches	A 2-hour headache response was achieved in 48% of zolmitriptan-treated attacks as compared with 27% of placebo-assigned attacks (P <.0001). Zolmitriptan was superior to placebo in achieving a headache response as early as 30 minutes (18% versus 14%, P=.03) and at 1 hour (33% versus 23%, P <.001). Drug-related adverse events were reported in 16% of subjects receiving zolmitriptan and 9% of subjects receiving placebo.
Loder et al.[140]	Adults – 40.0 ± 10.6 (Zolmitriptan 2.5 mg); 42.7 ± 10.5 (Placebo). n=565 (482 female and 83 male)	Zolmitriptan 2.5 mg orally disintegrating tablets (ODT) Placebo Patients treated up to 2 migraine attacks	Zolmitriptan 2.5mg ODT demonstrated a significant pain-free rate vs. placebo at 2h (40% vs. 20%, p < 0.001), 1.5h (25% vs. 15%, p < 0.001), and 1h (13% vs. 8%, p = 0.004). Sustained pain-free rate was significantly higher than placebo (31% vs. 15%; p < 0.001). Significantly more patients treated with zolmitriptan 2.5 mg ODT were able to return to routine activities (work, school, or other daily activities) when compared with placebo at 1h (p = 0.004), 1.5h (p < 0.001), and 2h (p < 0.001). Zolmitriptan 2.5 mg ODT was well tolerated. Overall, 33% (92/282) of patients treated with zolmitriptan 2.5 mg ODT experienced adverse events versus 14% (41/284) of placebo-treated patients. The adverse events most commonly reported in patients treated with zolmitriptan 2.5 mg ODT were those commonly associated with the use of triptans, including dizziness, somnolence, paresthesia, tightness, and asthenia.
Maghbooli et al.[141]	Adults Ginger group – 33.9 ± 8.3 Sumatriptan Group – 35.1 ± 6.2 n=100 (71 female and 29 male)	Ginger 250 mg powder capsule Sumatriptan 50 mg capsule One capsulet upon headache onset	Frequency distribution of mean headache severity at 2 h after drug use demonstrated similar effectiveness for sumatriptan and ginger groups (P = 0.116). Comparing mean headache severity before and 2 h after treatment revealed a 4.7 unit reduction (according to VAS) in the sumatriptan group (P<0.0001) and a 4.6 unit reduction in the ginger group (P<0.0001).
Mannix et al.[23]	Adults – mean age Rizatriptan - 38 years Placebo - 37 years n=403 (Female only)	Rizatriptan 10mg tablet Placebo Single migraine attack	The primary endpoint for efficacy analysis was pain relief at 2h. 2h pain relief - Rizatriptan 70% vs 53% placebo (OR 2.11, 95% CI 1.34, 3.32, P = 0.001). 24h Sustained pain relief - Rizatriptan 46% vs Placebo 33% (OR 1.75, 95% CI 1.11, 2.77, P = 0.016).
Mannix et al.[23]	Adults - Rizatriptan - 37 years; Placebo – 37.5 n=399 (Female only)	Rizatriptan 10mg tablet Placebo Single migraine attack	The primary endpoint for efficacy analysis was pain relief at 2h. 2h pain relief - Rizatriptan 73% vs Placebo - 50% (OR 2.69, 95% CI 1.66, 4.36, P< 0.001). 24h Sustained pain relief - Rizatriptan 46% vs Placebo 33% (OR 1.74, 95% CI 1.08, 2.82, P = 0.024).
Marín et al.[142]	Addults – mean age 35.9 years n=42 (Male 3 and Female 39)	Eletriptan Relpax 80 mg oral Placebo oral and intranasal spray Tetracaina 0,80 mg intranasal spray single migraine attack	After 30 minutes of therapeutic intervention both groups were compared by an unpaired Student t to obtain an average pain in the tetracaine group and an average of 1,952 for the pain group eletriptan of 4.0, with p = 0.0115. The improvement in pain and quality of life were correlated by Pearson's method with the following results r = 0.7833 and p < 0.0001y for eletriptan group r = 0.5143, p = 0.0171.
Martínez et al.[41]	Adults - 18 to 65 years of age n=360 (271 women and 89 men)	Metamizole (0.5 and 1 g) oral Acetylsalicylic acid (1 g) oral Placebo	The pain intensity reduced steadily for all three active treatments in comparison with placebo up to 4h after administration. The analgesic efficacy of 0.5 and 1 g metamizol vs placebo was highly statistically significant for sum of pain intensity differences, maximum pain intensity difference, number of patients with at least 50% pain reduction, time to 50% pain reduction, maximum pain relief and total pain relief. A trend towards an earlier onset of a more profound pain relief of 0.5 and 1 g metamizol over 1 g Acetylsalicylic acid was noticed. Adverse events were experienced during the treatment phase of the study in all groups, but differences statistics were not observed. Global assessment of tolerability by the patients was good or satisfactory in more than 90% of all patients.
Massiou et al.[143]	Adults - aged 18 to 65 years n=257 (Female only)	Naratriptan 2.5 mg Placebo single migraine attack	A higher percentage of subjects in the naratriptan group (58%) reported complete pain relief 4 h after medication than in the placebo group (30%) (P < 0.001). Significant differences between the naratriptan and placebo groups and in favor of naratriptan were also found for: total pain relief at 2 h (P = 0.004), sustained pain-free response within 4–24 h (P < 0.001), absence of all associated symptoms at 2 and 4 h (P =0.004), ability to work and carry out daily activities at 2 h (P = 0.036), and patient overall satisfaction (P <0.001).
Mathew et al.[144]	Adults – mean age 41.2 years (SD = 9.6) n=682 (614 female and 68 male)	Naratriptan tablet 2.5, 1 and 0.25 mg Placebo Treat 4 migraine attacks	Headache relief 4 hours postdose occurred in 68% naratriptan 2.5 mg vs 57% naratriptan 1.0 mg vs 3% naratriptan 0.25 mg vs 33% placebo (p < 0.001 naratriptan 2.5 mg and 1 mg versus placebo or 0.25 mg). Headache was eliminated 4 hours postdose - 45% naratriptan 2.5 mg vs 33% naratriptan 1 mg, 20% naratriptan 0,25 mg and 15% placebo (p < 0.001 naratriptan 2.5 mg and 1 mg versus placebo or 0.25 mg).

Mathew et al.[145]	Adults - aged to 18 to 65 Eletriptan 40 mg – 41.1 (10.8) Sumatriptan – 41.8 (10.4) Placebo – 41.6 (10.6) n=2,072 (Female 1795 and 277 male)	Eletriptan 40 mg tablet Sumatriptan 100 mg capsules Placebo Single migraine attack	Headache response rates at 2 hours postdose were significantly higher for eletriptan 40 mg (67%) than for sumatriptan 100 mg (59%; P .001) and placebo (26%; P .0001). Eletriptan 40 mg consistently showed significant (P .01) efficacy over sumatriptan 100 mg across secondary clinical outcomes, including 1-hour headache response; 2-hour pain-free response; absence of nausea, photophobia, and phonophobia; functional improvement; use of rescue medication; treatment acceptability; and sustained headache response (P<0.05). Overall, treatment-related adverse events were low.
Mathew, Kailasam, Meadors[146]	Rizatripitan 10 mg - 39.0 ± 9.5 years; Placebo - 42.0 ± 7.2 years. n=112 (103 female and 9 male)	Rizatriptan 10 mg tablets Placebo Three migraine attacks	Pain-free response at 2 hours after early treatment was noted in 70% of attacks in the rizatriptan group and in 22% in the placebo group (P < .01). Pain-free response at 1 hour occurred in 45% and 8% attacks, respectively (P < .01). When the attacks were categorized by headache severity at the time of treatment, the pain-free response at 2 hours was higher for mild attacks than for moderate or severe attacks (P < .01). Sustained pain-free response after treatment was significantly higher for attacks treated with rizatriptan (60%) than for those treated with placebo (17%) (P < .001). Adverse events were reported in 62 attacks (29%) in the rizatriptan group and 15 attacks (14%) in the placebo group.
Mathew et al.[147]	Adults – mean age 40.4 years n=378 (328 female and 50 male)	Almotriptan 12.5 mg tablet Placebo Consecutive 3 migraine attacks	Pain free at 2 hours portdose for the 1st headache - (Almotriptan 37% vs Placebo 23.9% p=0,010). 2-hour pain relief (Almotriptan 59.9% vs Placebo 42.6% p<0.001) and modified 2-hour pain relief (Almotriptan 59.9% vs Placebo 42.6% p<0.001). Significant differences in pain free, pain relief and modified pain relief between almotriptan and placebo was also observed at 1 hour.
McGinley et al.[148]	Adults – mean age 40.0 (12.3) years. n=259 (84.6% female and 15.4% male)	Sumatriptan 22 mg nasal powder Sumatriptan 100mg tablets Treat up to 5 attacks	The primary outcomes for these analyses were migraine pain intensity and migraine related disability. Average pain intensity for Sumatriptan 22 mg nasal treated attacks was significantly lower than sumatriptan treated ones at all time points from 10 to 90 minutes (P < .05 for all). The mean portion of the models showed that Sumatriptan 22 mg nasal had significantly lower disability from 10 to 90 minutes.
Meredith, Wait, Brewer[149]	Adults - mean age of 33 years (18 -54 years) n=29 (4 male and 25 female)	Sumatriptan 20 mg nasal Ketorolac 30 mg intravenous Sigle migraine attack	Patients scored the severity of their headache on a 100-mm visual analog scale (VAS) of pain prior to medication and again 1 hour after medication. Differences between initial and 1-hour scores were analyzed. Before treatment, no difference existed between the groups in the intensity of headache. One hour after medication, the sumatriptan group had a decrease in pain score of 22.937 mm and the ketorolac group a decrease of 71.462 mm on the VAS. The decrease in pain score with ketorolac was significantly greater than that with sumatriptan (P < 0.001).
Miljkovic et al.[150]	Adults - 18 to 64 years n=201 (168 female and 33 male)	Sumatriptan tablet Ergotamine combination tablet (propyphenazone, caffeine, camylofin chloride, mecloxamine citrate) Placebo	Higher percentage of patients was completely free of the headache 2 hours after dose administration in the ergotamine-based medication group compared to the sumatriptan group, regardless whether all (51.12 % vs 33.70 %) or only repeated attacks were taken into account (50.91 % vs 23.73 %). The salvage therapy (diclofenac) utilization rate was also lower in the ergotamine-based medication group (relative risk 0.61).
Misra et al.[151]	Adults - mean age of 32.6 ± 2.57 years. n=40 (Female 27 and Male 13)	Naproxen 500mg Sumatriptan 50 mg Rizatriptam 10 mg Ergotamine tartrate (2 mg) + caffeine (100 mg) + cyclizine HCL (50mg) Single dose during migraine attack	Naproxen, rizatriptan and sumatriptan were better than ergotamine in causing freedom from the associated symptoms of nausea, vomiting, photophobia and phonophobia at 2-hour postdose. Naproxen, rizatriptan and sumatriptan were also efficacious in causing functional normalization at 2 hours postdose as compared to ergotamine.
Misra, Kalita, Yadav[152]	Adults - Rizatriptan 29.15± 8.7, Ibuprofen 30.5 ± 10.6 and control 31.78 ± 9.9 years n=155 (female 114 and 41 male)	Rizatriptan 10 mg, Ibuprofen 400 mg Placebo Single migraine attack	Efficacy was assessed by headache relief and headache freedom at 2h and 24h. Two-hour headache relief was noted in 73% in rizatriptan, 53.8% in ibuprofen and 8% in placebo groups. Headache freedom was achieved in 37.7% in rizatriptan, 30.8% in ibuprofen and 2% in placebo groups.
Monda et al.[153]	Adults - 34,6 years (SD 9,6) n=101 (73 female and 28 male)	Indomethacin 25 mg + prochlorperazine 4mg and caffeine 75 mg suppository Sumatriptan 25 mg suppository Treatment of 4 consecutive migraine attacks	Pain-free at 2 hours postdose - Indomethacin 25 mg + prochlorperazine 4mg and caffeine 75 mg suppository was superior to sumatriptan in the second attack (52% versus 33%; P < .05) and in the total attacks (49% versus 34%; P < .01). The time to a pain-free response was significantly (P < .05) higher with Indomethacin 25 mg + prochlorperazine 4mg and caffeine 75 mg suppository than with sumatriptan in the first, second, and total attacks. Headache relief rates in the total attacks at 2 hours postdose were 71% with Indomethacin 25 mg + prochlorperazine 4mg and caffeine 75 mg suppository and 65% with sumatriptan, without any statistically significant difference between the drugs.

Moon et al.[154]	Adults - aged 18 to 65 years - frovatriptan: 36.75±10.23 years; placebo: 38.07±9.22 years. n=229 (207 females and 22 males)	Frovatriptan 2.5 mg Placebo	Frovatriptan significantly increased the 2-hour headache response rate compared with placebo (52.9% vs. 34.0%, p=0.004). The headache response rates at 4, 6, and 12 hours were significantly higher in the frovatriptan group than in the placebo group, as was the pain-free rate at 2 hours (19.0% vs. 5.7%, p=0.004), 4 hours (40.7% vs. 23.0%, p=0.006), and 6 hours (56.1% vs. 34.0%, p=0.002). The median time to a headache response was significantly shorter in the frovatriptan group than in the placebo group (2.00 hours vs. 3.50 hours, p<0.001). The use of rescue medications was more common in the placebo group (p=0.005).
Moshtaghion et al.[155]	Adults - sumatriptan group 33.36 + 7.91 and Propofol group 33.08 + 8.12 years n=90 (68 female and 22 male)	Sumatriptan 6 mg SC Propofol IV in 30 to 40 mg bolus Single migraine attack	Pain intensity was significantly lower in the propofol group 30 minutes after treatment (P = 0.001); however, after 1 and 2 hours, there were no significant differences between the groups. The need for antiemetic therapy and the recurrence of symptoms were significantly lower in the propofol group (P = 0.045 and P = 0.001, respectively).
Muller, Lohse[156]	Adults - Men = 45.31 ± 13.89 years; Women = 41.98 ± 12.54 years n=57 (13 male and 44 female)	Parecoxib 40 mg infusion Sumatriptan (6 mg/0.5 mL) Rizatriptan ODT 10 mg Single migraine attack	Rizatriptan decreased pain intensity 20 minutes after intake, (44.33; P<0.0001; post hoc analysis) more than parecoxib and sumatriptan, but parecoxib was more efficacious than sumatriptan. At 30 minutes after drug application, rizatriptan was superior (26.51; P<0.0001; post hoc analysis) to parecoxib and sumatriptan, but parecoxib showed a better effect on pain symptoms than sumatriptan.
Mushet et al.[24]	Adults - 40 (18 to 65) years (sumatriptan - 40.4 years and placebo - 37.9 years) n=80 (69 female and 11 males)	Sumatriptan 6 mg SC Placebo Single migraine attack	By 120 minutes after SC dosing, 73% of sumatriptan-treated patients compared with 28% of placebo-treated experienced headache relief (P≤0.05). Clinical disability scores 120 minutes after dosing showed that 75% of sumatriptan-treated patients, compared with 30% of placebo-treated patients, were normal or only mildly impaired (P≤0.05). Similar efficacy rates were observed for nausea, phonophobia, and photophobia. No serious or unusual adverse events occurred, and no clinically relevant abnormalities in laboratory test values were reported.
Mushet et al.[24]	Adults - 40 (18 to 65) years: sumatiptan: 40.2 years; placebo: 40.2 years. n=78 (10 males and 68 females)	Sumatriptan 6 mg SC Placebo Single migraine attack	By 120 minutes after SC dosing, 79% of sumatriptan-treated patients, compared with 37% of placebo-treated patients experienced headache relief (P≤0.05). Clinical disability scores 120 minutes after dosing showed that 85% of sumatriptan-treated patients, compared with 42% of placebo-treated patients, were normal or only mildly impaired (P≤0.05). Similar efficacy rates were observed for nausea, phonophobia, and photophobia. No serious or unusual adverse events occurred, and no clinically relevant abnormalities in laboratory test values were reported.
Myllylä et al.[157]	Adults - Tolfenamic Acid Rapid Release - 39±8.3 years; Placebo - 39±9.5 years; Sumatriptan - 40±10.0 years. n=140 (126 female and 14 male)	Tolfenamic acid rapid release tablets 200 mg Sumatriptan 100 mg oral Placebo Two successive migraine attacks.	For first attack, 77% of patients receiving tolfenamic acid experienced a reduction of the initial severe or moderate headache to mild or no headache after 2 hours, as compared to 79% in the sumatriptan group and 29% in the placebo group. No significant difference was found between active treatments (P = 0.85, 95% CI [-22%, 18%]), however, both active treatments were significantly better than placebo; P = 0.001, 95% CI (26%, 69%) for tolfenamic acid and P = 0.001, 95% CI (28%, 71%) for sumatriptan. For second attack, results were similar with 70% of patients receiving tolfenamic acid experiencing relief, as compared to 64% in the sumatriptan group and 39% in the placebo group. No significant differences were observed in accompanying symptoms. Both drugs were well tolerated with the frequency of adverse events; 30% for tolfenamic acid and 41% for sumatriptan (nonsignificant difference).
Nappi et al.[158]	Adults - 18 and 65 year; mean age 38 (11) placebo and Sumatriptan 38 (9). n=244 (188 female and 56 male)	Sumatriptan 100 mg tablet Placebo First dose at the earliest sign of migraine	Sumatriptan was significantly more effective than placebo at relieving headache (defined as reduction in severity from severe or moderate pain to mild or no pain) at 2 h (51% versus 31%, P = 0.003) and 4 h (71% versus 35%, P < 0.001). Fewer sumatriptan-treated patients required a second dose compared with placebo-treated patients (49% versus 74%, P < 0.001). More sumatriptan treated patients were completely pain free compared with placebo-treated patients at both 2 h (24% versus 12%) and 4 h (48% versus 18%).
Nett et al.[159]	Adults - Placebo = 36.8 ± 7.7; Sumatriptan 50mg = 35.3 ± 7.8; Sumatriptan 100mg = 37.1 ± 8.8. n=349 (Female only)	Sumatriptan 50 and 100 mg tablet Placebo Single menstrually associated migraine	Sumatriptan was superior to placebo in providing patients with pain-free relief at 2 hours. Pain-free relief at 2 hours - sumatriptan 100mg (61%) and sumatriptan 50mg (51%) compared with the placebo (29%) (both P <0.001). Sustained pain-free - Sumatriptan 100mg (31%) and 50mg (30%) compared with Placebo (14%) (100 mg versus placebo P =0.004; 50 mg versus placebo P= .007).

Newman et al.[160]	Adults - Naratriptan 2.5mg – 36.3 Naratriptan 1mg - 38 Placebo – 36.4 n=206 (all female)	Naratriptan 1 and 2.5mg oral Placebo Menstrual associated migraine	Headache-free Naratriptan 1mg 50% versus Placebo 25%, (P=.003). More patients treated with naratriptan 1 mg were headache free compared with placebo (23% versus 8%), although statistical tests were not performed. Significantly more patients treated with naratriptan 1 mg reported menstrual associated migraine 50% or less compared with placebo-treated patients. Patients treated with naratriptan 1 mg, also had significantly fewer menstrual associated migraine days compared with placebo-treated patients.
The Finnish Sumatriptan Group and the Cardiovascular Clinical Research Group[161]	Adults - 18-60 years [sumatriptan: 38±10; placebo: 40±9;] n=74 (11 male and 63 female)	Sumatriptan (insufflation 20 mg plus 20mg) Intranasal Placebo	Sumatriptan (20 mg plus 20 mg) was more effective than placebo at relieving headache, defined as reduction in severity from moderate or severe to mild or none, at 60 and 120 min. At 120 min, 75% of patients in the sumatriptan group reported headache relief, compared with 32% of patients in the placebo group ($p<0.001$); 53% of patients in the sumatriptan group were completely pain-free compared with 11% in the placebo group. Nausea incidence was significantly lower in sumatriptan group compared with placebo at both 60 min (17 vs. 43%; p=0.014) and 120 min (14 vs. 38%; p=0.021). Photophobia was significantly lower in sumatriptan group, compared with placebo at 60 min (28 vs. 57%; p=0.013) and 120 min (19vs. 51%; p=0.005). Sumatriptan was significantly more effective at reducing functional disability of patients at 30 min (p=0.024) and at 60 and 120 min ($p<0.001$). However, similar number of patients reported migraine recurrence, within 24 h in both treatment groups.
The Subcutaneous Sumatriptan International Study Group[162]	Adults - (41±11 years sumatriptan 6 mg; 40±11 years sumatriptan 8 mg; 39±11 years placebo) n=639 (521 females and 118 males)	Sumatriptan 6 or 8 mg SC Placebo	After 60 minutes, the severity of headache was decreased in 72% of the 422 patients given 6 mg of sumatriptan, 79% of the 109 patients given 8 mg of sumatriptan, and 25% of the 105 patients given placebo. As compared with the placebo group, 47% more patients who had received 6 mg of sumatriptan and 54% more patients who had received 8 mg of sumatriptan had a decrease in the severity of headache ($P<0.001$ for both comparisons). After 120 minutes, 86 to 92% of the 511 patients treated with sumatriptan had improvement in the severity of headache, as compared with only 37% of the 104 patients who received placebo once or twice ($P<0.001$ for all comparisons).
The Multinational Oral Sumatriptan and Cafergot Comparative Study Group[163]	Adults - mean age: 39.5 years [sumatriptan: 39±10 years; cafergot: 40±10 years;] n=577 (98 males and 479 females)	Sumatriptan 100 mg oral Cafergot (ergotamine tartrate 2 mg + caffeine 200 mg) capsules Three migraine attacks	Sumatriptan was significantly more effective than Cafergot at reducing the intensity of headache from severe or moderate to mild or none; 66% (145/220) of those treated with sumatriptan improved by 2 h, compared with 48% (118/246) of those treated with Cafergot ($p < 0.001$). The onset of headache resolution was more rapid with sumatriptan, whereas recurrence of migraine headache within 48 h was lower with Cafergot. Sumatriptan was also significantly more effective at reducing the incidence of nausea ($p < 0.001$), vomiting ($p < 0.01$) and photophobia/phonophobia ($p < 0.001$) 2h after treatment, and fewer patients on sumatriptan (24%) than on Cafergot (44%, $p < 0.001$) required other medication after 2h. The overall incidence of patients reporting adverse events was 45% after sumatriptan and 39% after Cafergot; the difference was not significant.
Pascual et al.[164]	Adults - Rizatriptan 10mg 38.5 years; Zolmitriptan 2.5mg 39.4 years; Placebo 38.2 years. n=766 (639 female and 127 male)	Rizatriptan 10mg tablet Zolmitriptan 2.5mg tablet Single migraine attack	The primary efficacy endpoint was pain free within 2h. Rizatriptan was superior to zolmitriptan, a HR = 1.26, rizatriptan was 26% more likely to be eliminated in the next few minutes than in a patient taking zolmitriptan. Headache relief at 2h - Rizatriptan 70.5% vs Zolmitriptan 66.8% vs Placebo 29.5%. Headache recurrence at 24h - Rizatriptan - 28%, Zolmitriptan 29% and placebo 26%.
Pascual et al.[165]	Adults - placebo 41.2 years (19±63); Almotriptan 6.25 mg 40.8 years (19±66); Almotriptan 12.5 mg 41.9 years (18±65). n=909 (788 female and 121 male)	Almotriptan 6.25 and 12.5 mg tablet Placebo Three consecutive migraine attacks	The total number of attacks relieved (severe or moderate pain reduced to mild or no pain) at 2 h post-dose was significantly higher ($P<0.001$) after treatment with almotriptan 6.25 or 12.5 mg compared with placebo (60% and 70% vs. 38%, respectively). Moreover, a consistent response was achieved across and within patients for almotriptan 6.25 or 12.5 mg compared with placebo (pain relief in at least 2 out of 3 attacks within 2h for 64% and 75% vs. 36%, respectively) and less than one-third of the patients relapsed within 24h. Almotriptan was well tolerated with no significant differences between the almotriptan and placebo treatment groups in the percentage of patients reporting adverse events.

Pascual et al.[166]	Adults - 33.7 years (16–66) n=481 (399 female and 82 male)	Rizatriptan 10mg (rapidly disintegrating tablets) Sumatriptan 50mg (tablets) Single migraine attack	The patients preferred rizatriptan 10mg rapidly disintegrating tablet to sumatriptan 50mg tablet (64.3 vs. 35.7%, p < or = 0.001). Faster relief of headache pain was the most important reason for the preference, cited by 46.9% of patients preferring rizatriptan and 43.4% of patients who preferred sumatriptan. Headache relief at 2h was 75.9% with rizatriptan and 66.6% with sumatriptan (p < or = 0.001), with rizatriptan being superior to sumatriptan within 30 min of dosing. Fifty-five percent of patients were pain free 2 h after rizatriptan, compared with 42.1% treated with sumatriptan (p < or = 0.001), rizatriptan being superior within 1 h of treatment. Forty-one percent of patients taking rizatriptan were pain free at 2 h and had no recurrence or need for additional medication, compared to 32.3% of patients on sumatriptan. Rizatriptan was also superior to sumatriptan in terms of the proportions of patients with no nausea, phonophobia or photophobia, and patients with normal function 2h after treatment intake (p < 0.05). More patients were satisfied 2 h after treatment with rizatriptan (73.3%) than 2 h after treatment with sumatriptan (59.0%) (p < or = 0.001). Both active treatments were well tolerated. The most common side effects with rizatriptan and sumatriptan were nausea (6.6 and 6.9% of patients, respectively), dizziness (6.1 and 5.8%) and somnolence (7.4 and 6.7%).
Pini et al.[167]	Adults - mean age 37.0 years, range 18 – 65 years). n=238 (52 males and 186 females)	Sumatriptan 100 mg oral Placebo Single migraine attack	Reduction in headache intensity - sumatriptan 65% versus placebo 40%. Reductions in accompanying symptoms of migraine - nausea/vomiting (33 versus 53%) and photophobia/phonophobia (37 versus 62%), respectively. Sumatriptan was very effective in reducing headache severity in patients with a history of prolonged migraine attacks (sumatriptan 67% versus 26% placebo).
Pini et al.[168]	Adults - male 33.6± 10.5 and female 35.6 ±9.6 years. n=92 (Male 31 and Female 61)	Paracetamol 1000mg + caffeine 130 mg sachet Sumatriptan 50 mg soft gel capsule Two migraine attacks	There was no difference between the two treatments regarding total pain relief pain during the 4-hour observation period.
Rahimdel et al.[169]	Adults - sodium valproate 31.3±3.5 years, Sumatriptan 6 mg 30.1±3.1 years. n=90 (67 female and 23 male)	Sodium valproate 400 mg IV Sumatriptan 6 mg SC Single migraine attack	In both groups, pain decrement at the mentioned time points was significant (P<0.001) but had no significant difference (P>0.05), indicating the similar effect of both drugs on pain improvement. In the Sodium valproate group, photophobia, phonophobia, nausea, and vomiting were improved significantly, while in the Sumatriptan group, only photophobia and vomiting were decreased significantly. Nausea, vomiting, facial paresthesia, and hypotension were more significantly frequent in the Sumatriptan group than in the Sodium valproate group (P<0.05).
Rao et al.[170]	Adults - 36.3±9.8 years n=54 (Female 98.1 % and Male 1.9 %)	Ketorolac nasal spray 31.5 mg Sumatriptan nasal spray 20 mg Placebo At least one attack	Both ketorolac (72.5%, P< .001) and sumatriptan (69.4%, P= .001) were more effective than placebo (38.3%) for 2-hour pain relief and 2-hour pain freedom (ketorolac: 43.1%, P= .004; sumatriptan: 36.7%, P= .046; placebo: 18.4%). Ketorolac but not sumatriptan was more effective than placebo in 2-hour absence of nausea. Both ketorolac and sumatriptan were more effective than placebo for 24-hour sustained pain relief (ketorolac: 49%, P< .001; sumatriptan: 31%, P= .01, placebo: 20%). Only ketorolac was superior to placebo for 24-hour (ketorolac: 35.3%, P=.003; sumatriptan: 22.4%, P= .18, placebo: 12.2%) sustained pain freedom. Nasal burning and dysgeusia were the most common adverse effects for active treatments.
Rapoport et al.[171]	Adults - 18 to 65 years (sumatriptan 6mg+placebo: 42.3 years; sumatriptan-6mg+100mg:42.5 years) n=667 (118 male and 549 female)	Sumatriptan 6 mg SC + Sumatriptan 100 mg (oral - 4hs later) Sumatriptan 6 mg SC + Placebo (oral - 4hs later) Three migraine attacks	The primary efficacy endpoint was the number of successfully treated patients without headache recurrence (HR) within 24 hours after the initial SC injection for the first study attack. 237/317 patients who received oral sumatriptan at 4 hours (75%) and 249/312 patients who received placebo at 4 hours (80%) reported no or mild headache pain at 2 hours after the initial open dose of 6 mg SC sumatriptan. By 4 hours, relief was reported by 78% of the patients who received oral sumatriptan and 82% of the patients who received placebo. Of 442 assessable patients, 82/212 in the sumatriptan-treated group (39%) and 89/230 in the placebo-treated group (39%) reported HR in attack 1. Median times to recurrence were 15.6 hours after sumatriptan and 10.3 hours after placebo (p = 0.006). After placebo, 58% of the recurrences occurred within 12 hours, compared with only 32% within 12 hours after sumatriptan. Similar results were observed for attacks 2 and 3.

Rapoport et al.[172]	Adults 41.3 ± 9.5 (12-66) years. n=999 (123 Male and 876 Female)	Zolmitriptan 1, 2.5, 5, or 10 mg Placebo Oral Single migraine attack	The headache response rates with zolmitriptan doses ≥ 2.5 mg were 44 to 51% at 1 hour, 65 to 67% at 2 hours, and 75 to 78% at 4 hours (all significantly superior to placebo). Also, zolmitriptan effectively relieved migraine-associated symptoms such as nausea, photophobia and phonophobia, and reduced activity impairment. Rates of headache recurrence, headache persistence, and use of escape medication were lower with zolmitriptan doses ≥ 2.5 mg than with placebo. In patients with persistent or recurrent headache, a second zolmitriptan dose effectively treated both headache and nonheadache symptoms.
Rothner et al.[173]	Adolescents - aged 12 to 17 years (14.2±1.7 years zolmitriptan 10 mg; 14.3±1.7 years zolmitriptan 5 mg; 14.3±1.7 years zolmitriptan 2.5 mg; 14.2±1.7 years placebo) n=696 (408 females and 288 males)	Zolmitriptan 2.5, 5, or 10 mg oral tablet Placebo Single migraine attack	There was no statistically significant improvement between zolmitriptan 10 mg (2 x 5 mg tablet) and placebo for the primary efficacy variable headache response at 2 hours, nor any of the secondary variables tested. Two-hour headache response rates were 54%, 53%, and 57% for zolmitriptan 10, 5, and 2.5 mg, respectively, and 58% for placebo. Two-hour pain-free rates were 25%, 19%, and 23% for zolmitriptan 10, 5, and 2.5 mg, respectively, and 20% for placebo. Zolmitriptan was well tolerated, with a tolerability profile similar to the pattern seen in adults.
Russell et al.[174]	Adults – mean age 44 years (±9.7 years) n=209 (females 189 and males 20)	Sumatriptan 6 mg SC Placebo Two migraine attacks	When sumatriptan was compared to placebo, significantly more of the 209 evaluable patients reported headache relief at 1 h (56% vs 8%, $p < 0.001$) and 2 h (62% vs 15%, $p < 0.001$) after the first injection. Resolution of nausea, photophobia, and phonophobia was significantly more common in patients on sumatriptan than in those on placebo ($p < 0.001$ for all comparisons).
Ryan et al.[25]	Adults - Suma 20mg -39.8/ Suma10mg – 40.4/ Placebo – 40.2 years. n=409 (58 male and 351 female)	Sumatriptan 20 and 10mg nasal spray Placebo One migraine attack	The primary efficacy endpoint was headache relief 120 minutes after the first administration of study drug. Headache relief - 62 to 63% patients in the sumatriptan 20-mg, 43 to 54% sumatriptan 10-mg, 29 to 35% of placebo ($p <0.05$). Pain-free 2h - 31 to 32% sumatriptan 20-mg groups, 20 to 23% sumatriptan 10-mg, 4 to 20% placebo ($p < 0.05$). Incidence of nausea, photophobia, and phonophobia reduced after sumatriptan 20mg ($p < 0.05$), sumatriptan nasal spray 10 mg compared with placebo reduced the incidence of nausea ($p < 0.05$).
Ryan et al.[25]	Adults - Suma20mg – 41.1/ Suma10mg – 41.2/ Placebo - 41.6. n=436 (63 male and 373 female)	Sumatriptan 20 and 10mg nasal spray Placebo One migraine attack	The primary efficacy endpoint was headache relief 120 minutes after the first administration of study drug. Headache relief - 62 to 63% patients in the sumatriptan 20-mg, 43 to 54% sumatriptan 10-mg, 29 to 35% of placebo ($p <0.05$ sumatriptan 20 mg vs placebo). Pain-free 2h - 31 to 32% sumatriptan 20-mg groups, 20 to 23% sumatriptan 10-mg, 4 to 20% placebo ($p < 0.05$ sumatriptan 20 mg and 10 mg vs placebo). Incidence of nausea, photophobia, and phonophobia reduced after sumatriptan 20mg ($p < 0.05$), sumatriptan nasal spray 10 mg compared with placebo reduced the incidence of nausea ($p < 0.05$).
Ryan et al.[26]	Adults - Frovatriptan 42.3 (SD 9.9 - Range 18 - 63)/Placebo 40.2 (SD 10.3 - Range 18 - 65) n=322 (42 male and 280 female)	Frovatriptan 2.5mg tablet Placebo Single dose	Response at 2 hours range from 27% to 46% for frovatriptan compared with 21% to 27% for placebo. Likewise, at 4 hours, frovatriptan was consistently significantly more effective than placebo to provide headache relief. Response forfrovatriptan ranged from 56% to 65% compared with 31% to 38% for placebo ($p<0,001$). Frovatriptan was also significantly superior to placebo at rendering patients pain-free. At 2 hours, the proportion of patients pain-free was 9% to 14% for frovatriptan compared with 2% to 3% for placebo ($p<0,001$). At 4 hours post dose, 27% to 32% of patients takins frovatriptan were pain-free compared with 9% to 14% in the placebo group ($p<0,001$).
Ryan et al.[26]	Adults - Frovatriptan 41.1 (SD 10 - Range 18 -69)/Placebo 41.1 (SD 10.4 - Range 18 - 69). n=1148 (131 male and 1017 female)	Frovatriptan 2.5mg tablet Placebo Patients could take up to 2 doses per attack for headache recurrence within 24 hours of the first dose	Response at 2 hours ranged from 27% to 46% for frovatriptan compared with 21% to 27% for placebo. Likewise, at 4 hours, frovatriptan was consistently significantly more effective than placebo to provide headache relief. Response for frovatriptan ranged from 56% to 65% compared with 31% to 38% for placebo ($p<0,001$). Frovatriptan was also significantly superior to placebo at rendering patients pain-free. At 2 hours, the proportion of patients pain-free was 9% to 14% for frovatriptan compared with 2% to 3% for placebo ($p<0,001$). At 4 hours post dose, 27% to 32% of patients taking frovatriptan were pain-free compared with 9% to 14% in the placebo group ($p<0,001$).

Ryan et al.[26]	Adults - Frovatriptan 41.1 (SD 10.4 - Range 18 - 69)/ Placebo 40.3 (SD 10.8 - Range 19 - 69). n=724 (106 male and 618 female)	Frovatriptan 2.5mg tablet Placebo Patients could take up to two doses per attack for headache recurrence within 24 hours of the first dose	Response at 2 hours ranged from 27% to 46% for frovatriptan compared with 21% to 27% for placebo. Likewise, at 4 hours, frovatriptan was consistently significantly more effective than placebo ar providing headache relief. Response for frovatriptan ranged from 56% to 65% compared with 31% to 38% for placebo (p<0.001). Frovatriptan was also significantly superior to placebo at rendering patients pain-free. At 2 hours, the proportion of patients pain-free was 9% to 14% for frovatriptan compared with 2% to 3% for placebo (p<0.001). At 4 hours post dose, 27% to 32% of patients taking frovatriptan were pain-free compared with 9% to 14% in the placebo group (p<0.001).
Sandrini et al.[174]	Adults - 18 to 65 years [placebo: 37.5±10.9; suma50mg: 37.4±10.2; suma100mg: 38.2±10.2; ele40mg: 38.0±10.1; ele80mg:39.9±10.7] n=774 (681 female and 93 male)	Eletriptan 40mg Eletriptan 80mg tablets Sumatriptan 50mg Sumatriptan 100mg Placebo gelatin capsules Multiple migraine attack	Headache response rates were 12% at 1 hour and 31% at 2 hours for placebo; 24% at 1 hour and 50% at 2 hours for sumatriptan 50 mg; 27% at 1 hour and 53% at 2 hours for sumatriptan 100 mg; 30% at 1 hour and 64% at 2 hours for eletriptan 40 mg; and 37% at 1 hour and 67% at 2 hours for eletriptan 80 mg. More patients receiving eletriptan 80 mg achieved a 1-hour headache response than did patients receiving sumatriptan 50 mg (p < 0.05). All doses of eletriptan were superior to sumatriptan at 2 hours for headache response and complete pain relief (p < 0.05). Significantly more patients on eletriptan 80 mg achieved headache response in all attacks than did patients receiving sumatriptan. Eletriptan 40 mg was superior to both sumatriptan doses in functional improvement (p < 0.005). The 40- and 80-mg doses of eletriptan were significantly more effective than placebo or sumatriptan in reducing the associated migraine symptoms of nausea, photophobia, and phonophobia after 2 hours. The 40- and 80-mg doses of eletriptan were significantly superior to oral sumatriptan or placebo in achieving and sustaining both headache response and pain-free response at 24 hours. The superior efficacy of both eletriptan doses was associated with higher rates of patient acceptability than sumatriptan 50 mg (p < 0.05). Eletriptan and sumatriptan were well tolerated.
Sandrini et al.[175]	Adults – mean age 35 ± 9.8 years n=281 (78% female and 22% male)	Sumatriptan 50mg tablets Indoprocaf-coated tablets Indoprocaf-effervescent tablets Two consecutive migraine attacks Indoprocaf - indomethacin, prochlorperazine and caffeine	Pain-free rates at 2 h (all attacks) - 34% Indoprocaf and 37% sumatriptan (p=NS). Headache relief at 2 h (all attacks) postdose - 62% Indoprocaf and 56% with sumatriptan (p=NS). Pain free 2h post first attack (indoprocaf coated-tablets vs effervescent tablets) - Indoprocaf-effervescent tablets 41% vs. Coated-tablets 22%(P<0.05). Headache relief rate at 2 h postdose in the first attack - Effervescent tablets 66% vs. Coated-tablets 49% (p < 0.05). Pain-free rate total attacks - Effervescent tablet 84% vs. Coated-tablets 73%. The total pain-free rate of Indoprocaf-coated tablets was lower than that of effervescent tablets, but higher than sumatriptan.
Sang et al.[176]	Adults - mean age 40 ± 9 years. n=44 (20 male and 24 female)	Ly293558 (nonselective AMPA/ KA (GluR5) receptor antagonist with 1.2 mg/kg IV Sumatriptan 6 mg SC Placebo Simgle migraine attack	The primary efficacy variable was the headache response rate, i.e. headache score improvement from moderate/severe at baseline to mild/none at 2 h. Response rates were 69% for LY293558 (P = 0.017 vs. placebo), 86% for sumatriptan (P < 0.01 vs. placebo) and 25% for placebo. LY293558 and sumatriptan were superior to placebo (P < 0.01 for all comparisons) on all other measures of improvement in pain and migraine associated symptoms. Fifteen percent of patients who took LY293558 reported adverse events, 53% patients who took sumatriptan and 31% of those who received placebo reported adverse events.
Santanello et al.[177]	Adults - Rizatriptan 10mg – 36.8 (SD 9); Rizatriptan 5mg – 37.6 (SD 8.2); Rizatriptan 2.5mg – 38.7 (SD 9.1); Placebo – 39.7 (SD 9.7) years n=247 (222 female and 25 male)	Rizatriptan 2.5, 5 and 10mg Placebo Oral One migraine attack	Statiscally significant mean improvements were observed for those treated with rizatriptan 10mg compared with those treated with placebo on three of five domains: social functioning (p=0,007), migraine symptoms (p=0.005), and feeling/concerns (p=0.015). Patients who took the 5-mg and 10mg rizatriptan doses were significantly less disabled as 2h than those who took placebo (p=0.003); however, the patients who took 2,5mg rizatriptan remained about as functionally disabled as patients on placebo.
Savi et al.[178]	Adults – 37±9 years n=125 (99 female 26 male)	Frovatriptan 2.5 mg Rizatriptan 10 mg Capsules Treat 1–3 attacks	Patient's preference for one drug or the other did not differ between the study treatments. Frovatriptan was chosen mainly because of the rapid speed of action (71% of patients), good tolerability (42% of patients), and reduction in pain severity (33%). A relevant result of study was that recurrence rate within 48 h were significantly lower under frovatriptan than under rizatriptan. These differences may be explained by the different pharmacokinetics of the two drugs. Frovatriptan has a time to maximum concentration typically of 2 to 3 h, but the longest half-life among triptans, greater 5-HT1B binding receptor potency, and multiple pathways metabolism. The headache recurrence was significantly less frequent with frovatriptan than under rizatriptan.

Savi, Mogavero, Egan.[179]	Adults – 39.4 ± 7.8 years n=18 (55.5% female and 44.4% male)	Frovatriptan 2.5 mg Rizatriptan 10 mg Two-treatmen migraine attack	The primary endpoint of interest was the correlation between plasma concentration of each triptan (and more specifically the concentration: maximum concentration (Cmax) ratio and the pain-free (PF) and pain-relief (PR) rates at each time point. PF 4h – Frovatriptan 38.4% vs Rizatriptan 5.6% (p=0.045). PR at 4h - Frovatriptan 61.1% vs Rizatriptan 72.2% (p=NS). There was a positive correlation between frovatriptan concentration: Cmax ratio (%) and the proportion of patients that were either pain free or experienced pain relief over the entire study period. No such correlation was seen for rizatriptan.
Schulman[180]	Adults – aged 18-66 years - mean (SD) 40.7 (11.2 (Transdermal Sumatriptan and 41.0 (11.0) Placebo. n=454 (male 68 and female 386)	Sumatriptan transdermal patch Placebo Single migraine attack	In the overall study population, transdermal sumatriptan was significantly superior to placebo at 1 hour post-activation for pain relief (29% vs 19%, respectively; P < .0135) and freedom from nausea (71% vs 58%, respectively; P < .05) and at 2 hours post-activation for freedom from pain (18% vs 9%, respectively; P < .009), pain relief (53% vs 29%, respectively; P < .0001), freedom from nausea (84% vs 63% respectively; P < .001), freedom from photophobia (51% vs 36%, respectively; P < .0028), freedom from phonophobia (55% vs 39%, respectively;P < .0002); and freedom from migraine (16% vs 8%, respectively;P < .0135). In the post-hoc analysis, transdermal sumatriptan was markedly superior to placebo for pain relief and freedom from pain, nausea, photo and phonophobia at 1 and 2 hours post-activation.
Scott et al.[181]	Adults – Group SS(S): 41.0 + 11.1 years; Group SS(P): 40.4 ±10.7 years; Group SP(S): 40.6 ±10.5 years; Group: SP(P): 42.1 ±10.6 years. n=1440 (214 male and 1226 female)	Sumatriptan 100 mg tablet oral Placebo Three migraine attack	Headache was relieved by the first sumatriptan dose in about 70% of patients, but the second dose did not produce significantly more relief than placebo, either in non-responders or in the group as a whole, nor did it reduce other symptoms (photophobia, nausea, vomiting, etc.) at 8 h, or influence the incidence of headache recurrence. The drug was well-tolerated, and a further single dose was effective in treating recurrence after initial relief. Of those patients who treated at least one attack and expressed a view of the treatment, 80% (n = 1056) said that they would take the medication again.
Seeburger et al.[182]	Adults – 43.8 years (20–68) [Riza/riza/placebo 43.3 years (20–68); Riza/placebo/riza 44.8 years (28–61); Placebo/riza/riza 43.5 years (23–64);] n=102 (female 88 and 14 male)	Rizatriptan 10 mg ODT tablet/oral lyophilisate Placebo Three migraine attack crossover	Pain relief at two hours was significantly greater with rizatriptan compared with placebo (51% vs. 20%, p<.001). Response rates also favored rizatriptan on two-hour pain freedom (22% vs. 12%, p=.013) as well as 24-hour sustained pain relief (38% vs. 14%, p<.001) and sustained pain freedom (20% vs. 11%, p=.036). Treatment was generally well-tolerated.
Seeburger et al.[183]	Adults – mean age 43.8 years (SD 11.6) (Range from 18 to 66). n=100 (92 female and 8 male)	Rizatriptan ODT 10 mg Placebo Multiple-attack study	The primary efficacy endpoint was the proportion of treated attacks resulting in pain relief at 2 hours postdose. Pain relief at 2h – Rizatriptan 55% of attacks vs Placebo 17%; odds ratio [OR] 5.80, 95% CI: [3.13,10.76], P < .001]. Secundary endpoints: sustained pain relief 2-24h and 2h pain freedom were also better in favor of rizatriptan.
Sheftell, Ryan, Pitman[184]	Eletrip 20mg - 41 (19-73); 40mg – 42 (18-78); 80mg – 41 (19-75); Placebo – 42 (18 – 69) years n=1190 (1037 female and 153)	Eletriptan 20, 40 and 80mg oral Placebo Three migraine attacks	A significantly higher proportion of patients treated with eletriptan reported a headache response at 2 hours compared to the placebo group (47%, 62%, and 59% for the 20-mg, 40-mg, and 80-mg doses, respectively, compared with 22% in the placebo group, P <0.0001 for all eletriptan doses).
Sheftell et al.[27]	Adults – Sumatriptan 100mg – 41.5 (SD 11.2); Sumatriptan 50mg – 41.6 (SD 10.8); Placebo – 41.2 (SD 10.8) years. n=1366 (1170 female and 196 male)	Sumatriptan 100mg tablets rapid release Sumatriptan 50mg tablets rapid release Placebo Single migraine attack	Using pooled data, the cumulative percentages patients with pain relief by 2 hours after dosing were 67% for sumatriptan tablets 50 mg and 72% for sumatriptan tablets 100 mg, compared with 42% for placebo (P < 0.001, both sumatriptan doses vs placebo). The cumulative percentages of patients with a pain-free response by 2 hours after dosing were 40% for sumatriptan tablets 50 mg and 47% for sumatriptan tablets 100 mg, compared with 15% for placebo.
Sheftell et al.[27]	Adults – Sumatriptan 100mg – 40.1 (SD 10.8); Sumatriptan 50mg 39.9 (SD 10.8); Placebo – 39.2 (SD 10.5) n=1330 (1126 female and 204 male)	Sumatriptan 100mg tablets rapid release Sumatriptan 50mg tablets rapid release Placebo Single migraine attack	Using pooled data, the cumulative percentages patients with pain relief by 2 hours after dosing were 67% for sumatriptan tablets 50 mg and 72% for sumatriptan tablets 100 mg, compared with 42% for placebo (P < 0.001, both sumatriptan doses vs placebo). The cumulative percentages of patients with a pain-free response by 2 hours after dosing were 40% for sumatriptan tablets 50 mg and 47% for sumatriptan tablets 100 mg, compared with 15% for placebo.

Silberstein et al.[185]	Adults – mean age 40 years n=1419 (female only)	Rizatriptan 5mg and 10 mg oral Placebo	In the subgroup of 335 women with menstrually associated migraine, rizatriptan was effective compared with placebo. At 2 hours after dosing, 68% of 139 women taking rizatriptan 10 mg and 70% of 115 women taking rizatriptan 5 mg with a menstrually associated migraine had pain relief compared with 44% of 81 patients taking placebo (P < .05). In all women, rizatriptan was as effective in treating menstrual as well as nonmenstrual migraine: 68% of 139 patients taking rizatriptan 10 mg with a menstrually associated migraine had pain relief at 2 hours after dosing compared with 69% of 393 patients with nonmenstrually associated attacks (test of menstrual association 5 nonsignificant; the analysis had 80% power to detect a difference of six percentage points between groups). Similar results were found for rizatriptan 5 mg (menstrual 70%, nonmenstrual 66%; not statistically significant).
Silberstein et al.[186]	Adults – 37.6 years (18 – 56) n=546 (female only)	Frovatriptan 2.5 mg tablet QD Frovatriptan 2.5 mg tablet BID Placebo Three-way crossover design	Use of frovatriptan reduced the occurrence of menstrually associated migraine. The incidence of menstrually associated migraine during 6-day was 67% for placebo, 52% for frovatriptan 2.5 mg QD, and 41% for frovatriptan 2.5 mg BID. Both frovatriptan regimens were superior to placebo ($p < 0.0001$), and the BID regimen was superior to the QD regimen ($p < 0.001$). Both frovatriptan regimens also reduced menstrually associated migraine severity ($p < 0.0001$), duration ($p < 0.0001$), and the use of rescue medication ($p < 0.01$ QD; $p < 0.0001$ BID) in a dose-dependent manner. The incidence and type of adverse events for both regimens were similar to placebo and consistent with those reported for short term migraine management.
Silberstein et al.[32]	Adults –18-65 years. n=275	Sumatriptan 22mg nasal powder Sumatriptam 100mg oral Two treatment sequences	Treatment with sumatriptan 22mg nasal powder provided greater reduction in migraine pain intensity, which was statistically significant vs oral sumatriptan in the first 30 minutes postdose, regardless of whether attacks were treated when pain was mild (least squares mean SPID-30 = 3.90 vs 0.24, P = 0.0013) or moderate/severe (least squares mean SPID-30 = 13.83 vs 10.07, P = 0.0002). At every time point from 15 to 90 minutes postdose, the proportion of attacks achieving total migraine freedom was greater and statistically significant after treatment with sumatriptan 22mg nasal powder vs 100 mg oral sumatriptan. Sumatriptan 22mg nasal powder treatment resulted in greater odds of achieving pain freedom (odds ratio, OR = 1.29, P< 0.01) and meaningful pain relief (OR = 1.32, P< .0001), which were also statistically significant compared with oral sumatriptan. In addition, a greater proportion of attacks treated with sumatriptan 22mg nasal powder vs oral sumatriptan was associated with sustained pain freedom, achieving statistical significance when assessed from 1 h postdose through 24 hours postdose (33.3% vs 27.9%; P < .05) and through 48 hours postdose (32.7% vs 27.4%; P< .05)
Smith et al.[187]	Adults - Sumatriptan 50 mg E + Naproxen sodium 500 mg - 42.5±11.0; Sumatriptan 50 mg E - 41.2±11.3; Naproxen sodium 500 mg - 42.1±10.7; Placebo - 41.2±10.2 years. n=972 (880 female and 92 male)	Sumatriptan 50 mg tablet Naproxen 500 mg tablet Sumatriptan 50 mg + Naproxen sodium 500 mg Placebo Single migraine attack	In the sumatriptan plus naproxen sodium group, 46% of subjects achieved 24-hour pain relief response (primary endpoint), which was significantly more effective than sumatriptan alone (29%), naproxen sodium alone (25%), or placebo (17%) (P < .001). Two-hour headache response also significantly favored the sumatriptan 50 mg plus naproxen sodium 500 mg therapy (65%) versus sumatriptan (49%), naproxen sodium (46%), or placebo (27%) (P < .001). A similar pattern of between-group differences was observed for 2-hour pain-free response and sustained pain-free response (P < .001). The incidence of headache recurrence up to 24 hours after treatment was lowest in the sumatriptan plus naproxen sodium group (29%) versus sumatriptan alone (41%; P = .048), versus naproxen sodium alone (47%; P = .0035), and versus placebo (38%; P = .08). The incidences of the associated symptoms of migraine were significantly lower at 2 hours following sumatriptan 50 mg plus naproxen sodium 500 mg treatment versus placebo (P < .001). The frequencies and types of adverse events reported did not differ between treatment groups, with dizziness and somnolence being the most common.
Solomon et al.[188]	Adults - Zolmitriptan 2.5 mg 40.7 ± 11.26 -Placebo 40.2 ± 11.84 years n=301 (45 male and 256 female)	Zolmitriptan 2.5 mg oral Placebo Single migraine attack	Patients treated a single moderate or severe migraine headache with 2.5 mg zolmitriptan or placebo and recorded clinical efficacy and adverse events on a diary form. Headache response at 2 hours was 62% for zolmitriptan compared with 36% for placebo ($p < 0.001$). At 4 hours, headache response was 70% with zolmitriptan and 37% with placebo ($p < 0.001$). Headache recurrence in patients treated with 2.5 mg zolmitriptan was 22% (versus placebo 30%). The headache response at 4 hours, pain-free rate, and response rate of nonheadache symptoms favored zolmitriptan over placebo.

Spierings et al.[189]	Adults - mean age 41.2 ±10.1 years (almotriptan) and 40.3 ± 10.1 (Sumatriptan) n=1173 (129 male and 1044 female)	Almotriptan 12.5 mg capsule oral Sumatriptan 50 mg capsule oral Single migraine attack	At 2 hours, almotriptan treatment provided headache relief in 58.0% of the subjects and sumatriptan treatment in 57.3%; headache freedom was provided by the medications in 17.9% and 24.6%, respectively (P =.005). Rescue medications were taken by 36.7% of the subjects in the almotriptan-treated group and by 33.2% in the sumatriptan-treated group; headaches returned to moderate or severe intensity in 27.4% and 24.0%, respectively. Treatment-emergent adverse events occurred in 15.2% of the subjects in the almotriptan-treated group and in 19.4% in the sumatriptan-treated group (P =.06); treatment-related adverse events occurred in 9.1% and 15.5% of the subjects, respectively (P =.001), including chest pain, which occurred in 0.3% and 2.2%, respectively (P =.004).
Spierings et al.[190]	Adults - mean age 42 years n=670 (female 580 and male 90)	Zolmitriptan 5 mg ODT Placebo Two migraine headaches	Zolmitriptan 5mg ODT was significantly more effective than placebo in achieving a headache response (reduction in migraine headache intensity from moderate or severe to mild or no pain) at 30 minutes (16.5% vs 12.5%; p = 0.048; primary endpoint), 1 hour (p < 0.0001), and 2 hours (p < 0.0001). Significantly more patients achieved a sustained headache response for 24 hours with zolmitriptan 5mg ODT than with placebo (42.5% vs 16.4%; p < 0.0001). Zolmitriptan 5mg ODT also produced a higher pain-free rate than placebo at all timepoints (0.5, 1 and 2 hours post-dose), with the differences becoming significant at 1 hour.
Spierings, Keywood[191]	Adults - 18 to 65 years n=496 (58 male and 438 female)	Frovatriptan 2.5mg oral Placebo 24-hour period	With regard to the first attack treated, 173 (36%) of the 486 subjects in the study did not take a second dose at 2 hours for nonresponse. At 2 hours and 4 hours, these "rapid responders" experienced a decrease in headache intensity from moderate or severe to mild or no pain in 84% and 98%, respectively ("headache response"). Six percent of them experienced a recurrence of moderate or severe headache within 24 hours following a response at 4 hours and 12% took rescue medication.
Stark et al.[192]	Adults – mean age 41.7 ± 8.7 years n=347 (female: 312 and male: 35)	Sumatriptan 50 mg oral during attack 1 Naratriptan 2.5 mg oral during attack 2 Placebo Two migraine attacks	Attack 1: About two thirds of this selected migraine population did not respond to sumatriptan. Attack 2: Naratriptan was statistically superior to placebo for headache relief at 2 hours and 4 hours, as well as for most other features of migraine attacks. These data suggest an intrinsic efficacy of naratriptan in this patient subset and not a coincidental response. No unexpected tolerability issues arose.
Stark et al.[193]	Adults - placebo: 42 (20 to 62) years; eletriptan 40 mg: 42 (18 to 68) years; eletriptan 80 mg: 42 (19 to 66) years. n=1153 (191 males and 962 females)	Eletriptan (40 mg and 80 mg) Placebo Oral Up to 2 doses of study medication	In the initial attack, significantly more eletriptan patients reported headache relief and complete pain relief at 2 h vs placebo (40 mg 62% and 32%, 80 mg 65% and 34%, placebo 19% and 3%; P < 0.0001). Headache relief occurred faster after eletriptan, with more patients at both doses reporting relief 30 min (40mg 8% , 80 mg 11% vs. placebo 2%, P<0.01 and P<0.001, respectively) and 1 h (33% of patients in both eletriptan groups vs. 9% in placebo group, P < 0.0001) after treatment than after placebo. There was a significantly lower recurrence rate with eletriptan 80 mg compared with placebo (80mg 21% vs. placebo 40%, P < 0.01). Treatment acceptability for patients taking one or two doses was high and signicantly better after either eletriptan 40 mg or 80 mg than placebo (78% and 83% vs. 38%, P<0.001 for each analysis).
Steiner et al.[194]	Adults - Eletriptan 40 mg - 40.3±10.4 (19-64) years; Eletriptan 80 mg - 40.4±10.5 (18–64) years; Zolmitriptan 2.5 mg - 40.1±10.5 (18–64) years; Placebo - 39.9±10.6 (19–61) years. n=1337 (203 male and 1134 female)	Eletriptan 80 mg Eletriptan 40 mg Zolmitriptan 2.5 mg Placebo Single migraine attack	The primary analysis was between eletriptan 80 mg and zolmitriptan. For the primary efficacy endpoint of 2-h headache response, rates were 74% on eletriptan 80 mg, 64% on eletriptan 40 mg, 60% on zolmitriptan (P < 0.0001 vs. eletriptan 80 mg) and 22% on placebo (P < 0.0001 vs. all active treatments). Eletriptan 80 mg was superior to zolmitriptan on all secondary endpoints at 1, 2 and 24 h, in most cases with statistical significance. Eletriptan 40 mg had similar efficacy to zolmitriptan 2.5 mg in earlier endpoints, and significantly (P < 0.05) lower recurrence rate and need for rescue medication over 24 h. All treatments were well tolerated: 30-42% of patients on active treatments and 40% on placebo reported all-causality adverse events that were mostly mild and transient.
Stronks et al.[33]	Adults - 42.2 years (SD 9.8; range, 20 to 59). n=12 patients	Naratriptan 2.5 mg tablet Naproxen 500 mg capsule To treat 2 migraine attacks	During the first hours after intake of the study medication, the objective behavioral parameeters showed no significant effect time and no significant differences between naproxen and naratriptan, but naratriptan showed improve of symptoms and the interval between treatment and relief was significantly shorter after intake of naratriptan.

Talabi et al.[195]	Sumatriptan – 26.8 (SD 4) Metoclopramide – 34.9 (SD 9) n=124 (77 male and 47 female)	Sumatriptan 6mg SC Metoclopramide 20mg IV Single migraine attack	At time 0 and 60 min, pain score with metoclopramide group were 6.74 ± 0.84 and 0.66 ± 0.59, respectively, according to the result of paired t-test. The other group showed similar results: baseline painscore in sumatriptan group was 6.12 ± 0.73 that decreased to 1.1 ± 0.70 after 60 min of treatment. Analysis with ANCOVA showed that the mean difference in T60 pain score between the two groups was 0.55 ± 0.13 (95% CI: 0.25-0.79 cm). This difference was statistically significant (P< 0.001).
Teall et al.[196]	Adults - Rizatriptan 10mg 40.7 ± 9.6; Rizatriptan 5mg 40.5 ± 9.6; Placebo 40.6 ± 10.5 years n=1218 (1055 female and 163 male)	Rizatriptan 10 and 5mg oral Placebo One migraine attack	The primary efficacy endpoint was the percentage of responders at 2 hours after the initial dose. Response rates at 2 hours - Rizatriptan 62% 5mg vs 71% 10mg vs 35% placebo (P<0.001). Pain-free at 1h - Rizatriptan 5mg 33% vs 10mg 42% vs Placebo 10%.Recurrence - Rizatriptan 44% 5mg vs 47% 10mg vs 40% placebo.
Tepper et al.[197]	Adults – mean age 41.3 (12-70 years) n=2,800 (2,399 female and 401 male)	Zolmitriptan 2.5 and 5mg tablets Placebo	The two-hour pain-free response rate was higher in patients who treated persistent headache of any intensity with any dose of zolmitriptan compared with placebo. However, there were no statistical differences between the two-hour headache response rate for 5mg, 2,5 mg of zolmitriptan or placebo.
Tepper et al.[198]	Adults - Placebo: 37.8 ± 12.0; Sumatriptan 25 mg: 37.9 ± 11.6; Sumatriptan 50 mg: 39.1 ± 12.2 and Sumatriptan 100 mg: 39.3 ± 11.4 years. n=400 (female 295 and male 105)	Sumatriptan 25mg, 50mg, 100mg tablets Placebo Single headache	At 2 hours, more patients treated with sumatriptan achieved headache relief, the primary efficacy measure, compared with placebo, but differences only approached statistical significance for 100 mg (P = .053). The 2-hour headache relief rate in the sumatriptan 25 or 50 mg groups was not significantly different than placebo. The time to use of rescue was significantly shorter in the placebo group compared with the sumatriptan 100 mg group (P = .002). The time to use of rescue in the sumatriptan 25 or 50 mg groups was not significantly different than placebo. More patients treated with placebo (22%) lost headache relief within 4 hours compared with patients treated with sumatriptan 25 mg (17%), 50 mg (14%), or 100 mg (7%).
Tfelt-Hansen et al.[199]	Adults - mean age (range): Placebo 39 (18-63); LAS+MTC 40 (18-62); Sumatriptan 39 (18-58) n=421 (female 327 and male 94)	Lysine acetylsalicylate oral (equivalent to 900 mg aspirin) and 10 mg metoclopramide (LAS+MTC) Sumatriptan 100 mg oral Placebo Two consecutive attacks with moderate or severe headache	LAS+MTC was as effective as sumatriptan with a decrease of headache from severe or moderate to mild or none of 57% and 53%, respectively, for the first migraine attack treated. Both treatments were better than placebo (success rate 24%, p<0,0001). LAS+MTC was significantly more effective in the treatment of nausea than sumatriptan (p<0,0001) and was better tolerated (adverse events in 18% and 28%, respectively, p<0;05)..
Tfelt-Hansen et al.[200]	Adults - 18 to 65 years, mean age: Placebo – 38.3 ± 10.3; Rizatliptan 5 mg - 38.3 ± 10.3; Rizatriptan 10 mg 37.0 ± 10.0; Sumatriptan 100 mg 39.2 ± 10.1. n=1099 (898 female and 201 male)	Rizatriptan 10 mg Rizatriptan 5 mg Sumatriptan 100 mg Placebo Oral	Headache relief rates after rizatriptan 10 mg were consistently higher than sumatriptan at all time points up to 2 hours, with significance at 1 hour (37% versus 28%, P = 0.010). All active agents were significantly superior to placebo with regard to headache relief and pain freedom at 2 hours (P < or = 0.001). The primary efficacy endpoint of time to pain relief through 2 hours demonstrated that, after adjustment for age imbalance, rizatriptan 10 mg had earlier onset than sumatriptan 100 mg (P = 0.032; hazard ratio 1.21). Rizatriptan 10 mg was also superior to sumatriptan on pain-free response (P = 0.032), reduction in functional disability (P = 0.015), and relief of nausea at 2 hours (P = 0.010). Significantly fewer drug-related clinical adverse events were reported after rizatriptan 10 mg (33%, P = 0.014) compared with sumatriptan 100 mg (41%).
Tfelt-Hansen et al.[201]	Adults - Male - Plac 48 (SD 10)/Sum 40 (SD 12); Female - Plac 36 (SD 11)/ Sum 36 (SD 9) n=101 (22 male and 79 female)	Sumatripan 50mg Placebo Single migraine attack	Pain-free at 2h - Sumatriptan 20/51 (39%) vs Placebo 8/45 (18%) [difference 21%; 95% confidence interval (CI): +4%–+39%; p=0.03, Fisher's exact test]
The oral Sumatriptan and Aspirin plus Metoclopramide Comparative Study Group[202]	Adults - Sumatriptan 100mg: 42 ± 12; Aspirin + metoclopramide: 39 ± 11 years n=355 (283 female and 72 male)	Sumatriptan ODT 100mg Aspirin 900 mg + metoclopramide 10 mg oral Up to three migraine attacks	The primary efficacy analisys was based on headache relief for attack1 from grande 3 or 2 to grade 0 or 1 after 2h . Pain relief 2h after attack 1 - Sumatriptan - 74/113 (56%) vs Aspirin+metoclopramide - 62/138 (45%) (p=0,078 NS). Pain-free - Sumatriptan 26% vs Aspirin+metoclopramide 14% (p=0.016) Pain relief 2h after attack 2 - Sumatriptan - 58% vs Aspirin+metoclopramide - 36% (p=0.001). Pain-free - Sumatriptan 23% vs Aspirin+metoclopramide 15% (p=NS). Pain relief 2h after attack 3 - Sumatriptan - 65% vs Aspirin+metoclopramide - 34% (p<0,001). Pain-free - Sumatriptan 34% vs Aspirin+metoclopramide 12% (p<0.001). Both treatments are equally effective at reducing nausea. There was no difference between treatments in the number of patients vomiting. Photophobia and phonophobia were relieved equally well within 2h by both treatments.

The Oral Sumatriptan International Multiple-Dose Study Group[203]	Adults – Placebo: 40 ± 10; Sumatriptan: 42 ± 10 years n=232 (34 male and 198 female)	Sumatriptan ODT 100mg Placebo	Patients who received sumatriptan showed a significantly (p<0.001) greater improvement in headache relief compared with the placebo group 2h after treatment (50 vs 19%, respectively) and more patients were pain-free (headache grade 0) in sumatriptan group at 2h (25 vs 5%) and at 4h (48 vs 13%). AT 2h fewer patients in the sumatriptan group experienced nausea, vomiting, photophobia/phonophobia. Headache recurred in 48% of patients receiving placebo and in 42% of sumatriptan-treated patients within 24h of the initial resolution headache. Adverse events were reported by 38% of patients in the sumatriptan-treated group compared with 23% in the placebo group (p=0.019).
The Sumatriptan Auto-Injector Study Group[204]	Adults - mean age 41 years n=235 (192 female and 43 male)	Sumatriptan 6 mg SC Placebo Single migraine attack	The primary measure of treatment efficacy was based on a comparison of the number of patients in the two treatment groups who had a reduction in headache severity from severe or moderate to mild or none at 1 and 2 h. At 1 h, 77% of patients treating with 6 mg sumatriptan compared to 26% treating with placebo (p<0.001) had mild headache or none. At 2 h, the response rates for all patients had risen to 83 and 30%, respectively. Of those patients requiring a second dose at 1 h, improvement to mild or no headache at 2 h was achieved in 61% of patients receiving sumatriptan compared to 15% of those receiving placebo.
Tietjen et al.[35]	Adults - 36.7 years (range 24 to 52 years) n=15 (female only)	Naratriptan 2.5 mg oral + Prochlorperazine 25 mg rectal suppository Naratriptan 2.5 mg oral + placebo Multiple migraine attack	Reduction in headache severity was observed at 2 hours (P < .001) and at 4 hours (P <.001) from headache onset, with no difference between the two treatment regimens (P = .34). A significant decrease in clinical disability at 2 hours (P < .001) and at 4 hours (P < .001) was observed, with no difference between the two treatment regimens (P = .28). The pain-free state at 4 hours was reported in a higher proportion with the naratriptan/placebo regimen (50% vs 25%), but the trial size would need to be doubled to significantly prove the endpoints. Resolution of adverse effects was similar with both regimens at 2 hours and at 4 hours, although nausea resolved more often for those using the naratriptan/prochlorperazine regimen.
Touchon et al.[205]	Adults – mean age 42 ± 10 years n=266 (36 male and 230 female)	Sumatriptan 6 mg SC Dihydroergotamine (DHE) nasal spray (1 mg plus optional 1 mg) Placebo Two migraine attack	Patients took SC sumatriptan for one attack and DHE nasal spray for the other in random order. Data from both treatment periods show that at all time points from 15 minutes, SC sumatriptan was significantly better than DHE nasal spray at providing both headache relief (moderate / severe headache improving to mild / none) and resolution of headache. Similarly, SC sumatriptan was superior to DHE nasal spray for the other efficacy end points assessed in the study. Patients reported that both treatments were well tolerated. Adverse events were reported by 43% of patients taking SC sumatriptan and 22% of patients taking DHE nasal spray, and these were usually mild and transient.
Tuchman et al.[206]	Adults – Zolmitriptan: 38.3 (20-51); Placebo: 38.7 (20-53) years n=334 (Female only)	Zolmitriptan 2.5mg tablet oral Placebo Menstrual migraine attacks	Primary efficacy endopoint was headache response at 2 hours after initial treatment, using a 4-point severity scale. 2-hour response: Zolmitriptan – 65.7% vs Placebo – 31.8% (p<0.0001). 4-hour response: Zolmitriptan – 81.7% vs Placebo – 57.9% (p<0.0001). Adverse events: Zolmitriptan – 62.9% vs placebo 26.7% - majority were mild or moderare intensity.
Tullo et al.[207]	Adults – mean age 38.3 ± 9.9 years. n=107 (85 female and 22 male)	Frovatripan 2.5mg Zolmitriptan 2.5mg Three migraine attacks	Patients (77%) expressed a preference for a triptan. Average preference - Frovatriptan – 2.9±1.3 vs Zolmitriptan – 3.0 ±1.3. Most common reasons - Rapid activity (83% F vs 72% Z), reduction of headache severity (53 F vs 42% Z) and no side efffects (40 F vs 40% Z).
Tullo et al.[34]	Adults - 38.6 ± 10 n=314 (272 female and 42 male)	Frovatriptan 2.5 mg Frovatriptan 2.5 mg + dexketoprofen 25 mg (FroDex25) Frovatriptan 2.5 mg + dexketoprofen 37.5 mg (FroDex37.5) oral At least one migraine attack	The proportions of subjects without pain at two hours (primary endpoint) were 29% (27/93) with Frovatriptam alone compared with 51% (48/95 FroDex25 and 46/91 FroDex37.5) with each combination therapies (p < 0.05). FroDex25 and FroDex37.5 showed a similar efficacy both for primary and secondary endpoints. It seems there is no dose response curve for the addition of dexketoprofen.
Tulunay et al.[34]	Adults – mean age 32.7 ± 8.7 years. n=56 (47 female and 9 male)	Dipyrone 1g mg (2 tablets of 500 mg) oral Placebo	Total pain relief and pain relief were primary outcomes. Pain relief at 2h - Dipyrone 59/112 (52.7%) vs Placebo 13/56 (23.2%) (p<0,01). At 4h - Dypirone 64/112 (57.1%) vs Placebo 16/56 (28.6%) (p<0.001). Total pain relief at 2h - Dypirone 42/112 (37.5%) vs Placebo 6/56 (10.7%) (p<0.001). At 4h - Dipyrone 45/112 (40.2%) vs Placebo 7/56 (12.5%) (p<0.001). Pain recurrence after total pain relief - Dipyrone 16.7% (7/42 attacks) and Placebo 33.3% (2/6 attacks).

Visser et al.[208]	Adults – Placebo: 39 (SD 10); Sumatriptan 1mg: 41 (SD 11); Sumatriptan 2mg: 40 (SD 11); Sumatriptan 3mg: 39 (SD 10). n=685 (165 male and 520 female)	Sumatripan 1, 2 and 3 mg SC Placebo One migraine attack	By 30 minutes post dose 17% (95% CI 8% to 27%) more patients had improved with 1 mg sumatriptan, 22% (95% CI 13% to 32%) with 2 mg sumatriptan and 34% (95% CI 24% to 44%) with 3 mg sumatriptan than with placebo ($p < 0.001$ for all three comparisons versus placebo). The number of patients who were improved increased significantly with increasing dose ($p < 0.002$; chi-square test for trend). Complete resolution of pain was obtained at 30 min by 5% of placebo-treated patients, 9% of patients treated with 1 mg sumatriptan and by 14% treated with 2 mg or 3 mg sumatriptan, respectively.
Visser et al.[209]	Adults - range: 18 to 55 years [Placebo: 39±9 years; Riza-10mg: 40±9 years; Riza-20mg: 40±8 years; Riza-40 mg - 41±9 years; Suma-100 mg: 41±10 years;] n=449 (402 female and 47 male)	Rizatriptan 10, 20, 40 mg Sumatriptan succinate 100 mg Placebo oral One migraine attack	The proportion of patients with headache relief was 18% for placebo; 46% for sumatriptan; and 52% for 10-mg, 56% for 20-mg, and 67% for 40-mg rizatriptan. All differences with placebo were statistically significant (P<.001), and 40-mg rizatriptan was superior to sumatriptan (P=.01). The proportion of patients who became free of pain at 2 hours was 3% for the placebo-treated group; 22% for the sumatriptan-treated group; and 26%, 35%, and 47% for the group of patients who took the 10-, 20-, and 40-mg doses of rizatriptan, respectively (all differences with placebo, P<.005; 40-mg rizatripan vs sumatriptan, P=.001). The recurrence of headache within 24 hours was found to be equal across all treatment groups—approximately 40%. Adverse events (most commonly short-lasting mild or moderate dizziness and drowsiness) occurred more frequently after a 40-mg dose of rizatriptan was given than after other treatments.
Visser et al.[53]	Adolescents - Rizatiptan 14.3 (SD 1.7) / Placebo – 14.1 (SD 1.8) years n=476 (264 female and 212 male)	Rizatriptan 5mg oral Placebo Single attack	Primary efficacy measure was 2h pain relief: Rizatriptan 68.2% vs Placebo 68.8% (P=NS). Considering just patients who treated migraine on weekend - Rizatriptan 74% vs Placebo 58.3% (p=0.022). There was no difference in adverse events - Rizatriptan 34.3% vs Placebo 30.2%.
Wang, Fuh, Wu[210].	Adults - Sumatriptan 20mg: 37.0 ± 10.8 years; Placebo: 37.4 ± 9.8 years. n=56 (48 female and 8 male)	Sumatriptan 20mg spray Placebo spray	A significant difference in headache relief rates between the 2 groups was observed at 30 minutes postdose (46% vs. 21%, $p < 0.05$). One-hour postdose, 61% of sumatriptan recipients experienced headache relief compared with 43% of placebo recipients ($p = 0.181$). The difference in relief rates between groups diminished over time, mainly due to a high placebo response (54% at 2 hours postdose). Nausea, photophobia and phonophobia were alleviated in the majority of patients in the sumatriptan nasal spray group, although the benefit in comparison to placebo did not reach statistical significance. Most of the adverse events reported in the sumatriptan group were mild and transient, and none were considered serious.
Wells, Steiner[211]	Adults - mean age 18 – 29 (13.9%); 30 – 45 (48.7%); >45 (37.4%) years n=674 (565 female and 109 male)	Eletriptan 40mg Eletriptan 80mg Placebo	Patients receiving either dose of the active compound were unable to perform their usual activities for a median period of 4 hours compared with 9 hours experienced by those taking placebo. This difference was highly statistically significant ($p < 0.001$). The time saving associated with eletriptan usage reflected the differences in efficacy findings in the clinical component of the study.
Wendt et al.[212]	Adults - Sumatriptan 4mg: 38.3 (SD 9.5 - Range 18-59) Placebo – 38.1 (SD 9.7 - Range 18-59). n=577 (501 female and 76 male)	Sumatriptan 4mg SC Placebo SC Single migraine attack	The primary efficacy measurement was pain relief at 2 hours. Pain relief at 2h: Sumatriptan 4mg - 70% (n = 268) and Placebo - 22% (n = 42) ($P < 0.001$). Pain free at 2h: Sumatriptan - 50% (n = 192) and placebo - 11% (n = 21) ($P < 0.001$). Use of rescue medication: Placebo - 45% (n = 86) Sumatriptan - 22% (n = 84). Adverse events: Sumatriptan - 66% (n = 265) and Placebo - 39% (n = 75) ($P < 0.001$).
Winner et al.[213]	Adults - DHE-45: 40.5±8.6 years and range of 20 to 63 years; sumatriptan: 41.5 years and range of 22 to 59 years. n=310 (272 females and 38 males)	Dihydroergotamine mesylate (DHE-45) 1 mg SC Sumatriptan succinate 6 mg SC Single migraine attack	At 2 hours, 73.1% of the patients treated with dihydroergotamine and 85.3% of those treated with sumatriptan had relief (P=.002). There was no statistical difference in headache relief between the groups at 3 or 4 hours. Headache relief was achieved by 85.5% of those treated with dihydroergotamine and by 83.3% of those treated with sumatriptan by 4 hours. By 24 hours 89.7% of dihydroergotamine-treated patients and 76.7% of sumatriptan-treated patients had relief (P=.004). Headache recurred within 24 hours after treatment in 45% of the sumatriptan-treated patients and in 17.7% of the dihydroergotamine-treated patients (P≤.001).

Winner et al.[54]	Adolescents - 14.1±1.6 (12 to 17) years; [Placebo -14.2±1.6, Suma-5mg 14.1±1.7, Suma-10mg 14.0±1.6, Suma-20mg 14.0±1.6] n=510 (250 male and 260 female)	Sumatriptan 5mg, 10mg, or 20mg nasal spray Placebo	Headache relief 1-hour postdose was significantly greater for patients using 10 mg (56%) and 20 mg (56%) of sumatriptan nasal spray compared with placebo (41%). Headache relief 2 hours postdose was significantly greater for patients using 5 mg of sumatriptan nasal spray (66%) compared with placebo (53%) and approached statistical significance for 20 mg (63%) compared with placebo (53%). Complete relief 2 hours postdose was significantly greater for patients using 20 mg of sumatriptan nasal spray compared with placebo (36% vs 25%, respectively). Photophobia and phonophobia were significantly reduced 2 hours postdose for sumatriptan nasal spray (20 mg), compared with placebo (36% vs 48% and 25% vs 44%, respectively). Taste disturbance was the most commonly reported adverse event (2%, 19%, 30%, and 26% for placebo, 5 mg, 10 mg, and 20 mg, respectively). No drug-related serious adverse events or clinically relevant changes were reported.
Winner et al.[55]	Adolescents – mean age 14 years n=296 (161 female and 135 male)	Rizatriptan 5mg oral Placebo	The percentage of patients pain-free at 2 hours was 32% for rizatriptan 5 mg versus 28% for placebo (P.474). The percentage of patients with pain relief (reduction of predose pain intensity to mild or none) at 2 hours was 66% for rizatriptan versus 56% for placebo (P.079). Compared with placebo, rizatriptan significantly improved functional disability at 1.5 and 2 hours, and nausea at 1 and 1.5 hours. Rizatriptan 5 mg was well tolerated. The most commonly reported adverse events among patients receiving rizatriptan were dry mouth, dizziness, asthenia/fatigue, nausea, and somnolence.
Winner et al.[28]	Adults – mean age 40.3 years (aged 18-65 years) - Placebo: 40.7±10.5 years; Sumatriptan-50 mg: 39.8±10.5 years; sumatriptan-100 mg 40.5±10.0 years. n=354 (311 females and 43 male)	Sumatriptan 50 mg and 100 mg tablets Placebo Single migraine attack	Significantly more patients treated with sumatriptan, 100 mg and 50 mg were pain-free relief at 2 and 4 hours after treatment vs patients treated with placebo (at 2 hours, 53% and 48% vs 29%; at 4 hours, 71% and 66% vs 32%; for both, P<.001). Also, significantly more patients treated with sumatriptan 50 mg and 100 mg were migraine-free (no pain or associated symptoms) vs those treated with placebo at 2 and 4 hours after treatment (at 2 hours, 41% and 48% vs 25%; at 4 hours, 58% and 66% vs 30%; for both, P<.001). The incidence of overall adverse events was low with the 50- and 100-mg dose of sumatriptan (placebo, 8%; sumatriptan at 50 mg, 18%; sumatriptan at 100 mg, 19%).
Winner et al.[28]	Adults - mean 42.6 years (aged 18-65 years) - Placebo: 42.7 ±9.8 years; Sumatriptan-50 mg: 43.5±10.4 years; sumatriptan-100 mg 41.7±11.0 years. n=337 (298 females and 39 males)	Sumatriptan 50 mg and 100 mg tablets Placebo Single migraine attack	Significantly more patients treated with sumatriptan 100 mg and 50 mg, with pain-free relief at 2 and 4 hours after treatment vs patients treated with placebo (at 2 hours, 62% and 53% vs 29%; at 4 hours, 65% and 55% vs 30%; for both, P<.001). The incidence of overall adverse events was low with the 50- and 100-mg dose of sumatriptan (placebo, 6%; sumatriptan at 50 mg, 9%; sumatriptan at 100 mg, 12%).
Winner et al.[47]	Adults – Sumatriptan: 40.2 (SD 9.7)/Placebo: 41.1 (SD 10.4) years n=297 (247 female and 50 male)	Sumatriptan 6mg SC Placebo	Pain-free 2h: Sumatriptan - 48% vs Placebo 18% (P < 0.001). Headache relief 2h: Sumatriptan 72% vs Placebo 32% (P < 0.001).
Winner et al.[47]	Adults – Sumatriptan: 38.8 (SD 10.1)/ Placebo: 39.3 (SD 9.7) n=287 (38 male and 249 female)	Sumatriptan 6mg SC Placebo	Pain-free 2h: Sumatriptan - 57% vs Placebo 19% (P < 0.001). Headache relief 2h: Sumatriptan 77% vs Placebo 41% (P < 0.001).
Winner et al.[45]	Adolescents - Sumatriptan 20mg: 14.3 ± 1.8 (12 - 18); Sumatriptan 5mg: 14.3 ± 1.6 (12-18); Placebo: 14.2 ± 1.7 (11-17). n=731 (400 female and 331 male)	Sumatriptan 20 and 5mg Nasal Spray Placebo Single migraine attack	The primary efficacy endpoints were headache relief rates at 1 hour and sustained relief rates from 1 to 24 hours postdose. Headache relief at 1 h: Sum nasal spray 20mg - 61% vs Sum nasal spray 5mg - 53% vs Placebo - 52% (p=0.087). Pain-free headache 2h: Sum nasal spray 20mg - 44% vs Placebo 30% (p<0.001). Sustained relief 1-24h - Sum nasal spray 20mg - 41% vs Sum nasal spray 5mg - 37% vs Placebo 32% (P=NS). Overall incidence of adverse events in each treatment group (8% placebo; 26% sumatriptan nasal spray 5 mg; 33% sumatriptan nasal spray 20 mg).
Winner et al.[46]	Adolescents – Eletriptan: 14 ± 1.65 years; Placebo: 14 ± 1.65 years n=274 (157 female and 117 male)	Eletriptan 40mg oral Placebo Single migraine attack	The primary outcome measure was 2-hour headache response. Headache response rates were almost identical on eletriptan 40 mg and placebo by 2 hours (57% vs 57%). Pain-free rates were also similar at 2 hours (22% vs 15%). Absence of associated symptoms at 2 hours eletriptan 40 mg and placebo, respectively, for nausea (75% vs 78%), photophobia (62% vs 64%), and phonophobia (70% vs 67%). Use of rescue medication for nonresponse was somewhat lower on eletriptan 40 mg than on placebo (32% vs 39%). Significant differences in efficacy - 24-hour outcomes measures: sustained headache response (52% vs 39%; P < .005) and sustained pain-free response (22% vs 10%; P < .005).

Winner et al.[29]	Adolescents - Zolmitriptan 5mg: 14.5 (SD1.67); Zolmitriptan 2.5mg: 14.6 (SD1.77); Zolmitriptan 0.5mg: 14.5 (SD 1.72); Placebo - 14.3 (SD 1.67). n=798 (305 male and 493 female)	Zolmitriptan 5, 2.5 and 0.5mg nasal spray Placebo Single migraine attack	The primary outcome variable is pain-freestatus 2 hours post-treatment. Pain-free 2 hours post treatment: Zolmitriptan nasal spray 5mg - 68/229 (29,7%) vs Placebo 42/253 (OR 2.18; 95% CI 1.40, 3.39 (16,6%) (P< .001). Headache response at 2h: Zolmitriptan nasal spray 5 mg 51% [116/229] vs Placebo 39% [99/253]; P =0.010. Sustained headache response 2h: Zolmitriptan (any dose) - 30% (120/396) vs Placebo 24% (59/251) - not statistically significant.
Zhang et al.[214]	Adults - Rizatriptan Group: 36.6±12.8 years; Propacetamol group: 35.6±10.8 years. n=148 (76 female and 72 male)	Propacetamol (1 g) IV Rizatriptan 5 mg oral	Propacetamol showed superior efficacy at 1 h and there was no significant difference at 30 min or at 2 h. This indicates that propacetamol is at least as effective as rizatriptan in the treatment of acute migraine attacks.

Discussion

Our study suggests that overall response to triptans is as effective as that observed with dipyrone in acute migraine treatment.

Several studies involving triptans have evaluated the efficacy of different doses compared to placebo or included an evaluation of comparative efficacy between different triptans or doses. In general, all types of triptan were more effective than placebo in relieving migraine, with a good safety standard, although some drugs have achieved similar results as those for placebo. Attention to exceptional positive results for placebo in migraine treatment in some double-blind studies should be given, especially in the adolescent population. Symptoms related to migraine (nausea and vomiting, phonophobia and photophobia) also had a good response with triptans. In general, triptans were effective in relieving associated symptoms and reducing clinical disability compared to placebo. A poor response to one triptan does not predict a poor response to other agents belonging to the class.

Regarding dipyrone (metamizole) results, Bigal showed that the number of patients required to be treated with dipyrone 1 g by intravenous injection compared to placebo for at least one to benefit was 3.3 in 30 min and 2.2 in 60 min. There were statistically significant reductions in recurrence (dipyrone = 25%, placebo = 50%) and use of rescue medication (dipyrone = 20%, placebo = 47.6%) for the dipyrone group.[38]

A few studies have evaluated the restoration of functional ability after a migraine crisis and, to a lesser extent, lost time from work. A good number of studies evaluated the possibility of returning to normal functions or the number of patients who were able to return to normal activities after an average of 2 hours from initial treatment for a migraine episode. All studies involved triptans and no study was performed with dipyrone.[24, 35, 36, 55, 68, 69, 73, 85, 129, 130, 135, 140, 143, 145, 152, 161, 166, 177, 211]

Barbanti et al evaluated equivalent work time loss after a migraine attack, and the results showed 1.9 ± 2.3 and 2.5 ± 4.7 hours lost from work for sumatriptan 100 mg and 50 mg, respectively, compared with 3.5 ± 4.3 for placebo. Sumatriptan 100 mg was also able to better restore functional ability.[64]

Freitag et al. (REF) evaluated normal function disability, bed rest required, and ER/hospitalization resulting from a migraine attack in order to compare almotriptan and placebo responses at 2h- and 4h-posttreatment. The study showed that pain resolution was associated with a normal level of function, and the absence of photophobia, phonophobia, and nausea at 2 hours was also associated with less disability. In the study, treatment with almotriptan compared with placebo resulted in consistently better 24-hour quality of life scores, with restored social function. A logistic regression model determined that pretreatment functional level and pretreatment pain intensity were significant covariates of the proportion of patients who achieved normal function at 2 hours posttreatment.[103]

Dasbacj et al.[84] demonstrated that rizatriptan decreased the total number of lost work hours by 1.1h per treated migraine attack compared with placebo.

Most studies that evaluated migraine in the menstrual period involved triptans.[97, 159, 160, 185, 206] Silverstein et al. demonstrated that treatment results with rizatriptan in menstrual period migraine were similar compared to those for migraine unrelated to the menstrual period.[185]

Some studies have associated hormonal drugs and mainly NSAIDs with the use of triptan in one of the tested arms, with good therapeutic results in general, especially when there was an association of a triptan with a NSAID, with superior results when compared to the drug alone. Naproxen, ketoprofen and ibuprofen were the most common NSAIDs evaluated in the studies.[20, 30, 33, 34, 48, 86, 106, 187]

Tullo et al. evaluated the factors that influenced the selection of a treatment for migraine, comparing frovatriptan and zolmitriptan in the selected study, and found the following order of priority: 1) speed of action; 2) reduction in pain intensity and 3) absence of side effects.[207] On the other hand, Savi et al.[178] demonstrated the following order of choice by patients: rapid speed of action, good tolerability and reduction in pain severity, being decisive for the selection of frovatriptan over rizatriptan. Although these studies have evaluated triptans, rapid pain relief appears to be the main attribute of drug selection for migraine relief.[92, 171, 207]

Regarding the question presented in this study: "what is the evidence for the efficacy and safety of metamizole for the treatment of migraines compared with triptans?" The result is that overall response to metamizole is as effective as that observed with triptans in acute migraine treatment. The second point of evaluation in this systematic review was: "how effective are those treatments in improving cognitive

dysfunction in patients with migraine?" Unfortunately, cognitive improvement is not a goal evaluated in most studies included in the review. A few triptan studies showed that pain resolution was associated with a normal level of function, and also a logistic regression model determined that pretreatment functional level and pretreatment pain intensity were significant covariates of the proportion of patients who achieved normal function at 2 hours posttreatment. There are no data regarding cognitive dysfunction improvement related to metamizole utilization, so it may just be an inference related to metamizole.

This systematic review involved different forms of administration and doses of metamizole and triptans, which allowed us to have a complete and comprehensive view of studies involving both studied medications in migraine treatment, but limits some more direct comparisons between doses and routes of administration. Most studies performed with triptans utilized oral administration and most studies with metamizole in this review utilized the intravenous route of administration.

No direct comparisons between metamizole and triptans have been performed in a controlled and randomized clinical study and most studies involving triptans have been conducted in European countries and the US.

The main weakness of this systematic review and meta-analysis is the small number of studies involving metamizole included. The literature on metamizole is scarce. In the setting of the present analyses, only 5 articles with metamizole had a placebo arm and the estimates obtained were all indirect. This fact is directly related to the absence of drug availability in expressive markets, such as the US and some European countries. Studies with metamizole included in this review were limited to Brazil, Spain and Turkey.[8, 37, 39-42]

Despite the adverse event of agranulocytosis being the main reason for metamizole withdrawal from the market in some countries, this health risk was not proven true in the pharmacovigilance data and other scientific evidence generated in countries that maintained product commercialization.[215-217]

The data did not show a significant difference between metamizole and triptans in neither pain relief nor pain absence 2 hours after medication. In support of relief within 24 hours after medication, eletriptan, rizatriptan and zolmitriptan showed statistically different proportions from metamizole. There is no evidence of a difference between metamizole and triptans in absence of pain 24 hours after medication.

Considering the equivalence of therapeutic benefit and adverse events with triptans, especially cardiovascular ones, in addition to pharmacoeconomic aspects, as metamizole is far cheaper than triptans, metamizole could be a good medicine option for migraine treatment.

Conclusion

Metamizole may be equally effective as triptans in acute migraine treatment, with a good tolerability profile and a potentially better cost-benefit ratio with significant implications to healthcare policies. More studies are necessary to confirm our results.

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Abbreviations
AEs, adverse effects
Bid, twice daily
CI, Confidence Interval
IV, intravenous
NS, nasal spray
NSAIDs, non-steroidal anti-inflammatory drugs
ODT, orally disintegrating tablet
PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols
qd, once daily
SC, subcutaneous
TDS: iontophoretic transdermal patch
US, United States

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