Oral triptans (serotonin 5-HT$_{1B/1D}$ agonists) in acute migraine treatment: a meta-analysis of 53 trials

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Summary

Background The triptans, selective serotonin 5-HT$_{1B/1D}$ agonists, are very effective acute migraine drugs with a well-developed scientific rationale. Seven different triptans will soon be clinically available, making evidence-based selection guidelines necessary. Triptan trials have similar designs, facilitating meta-analysis; this will provide a foundation for using triptans in clinical practice.

Method We asked pharmaceutical companies and the principal investigators of company-independent trials for raw patient data of all double-blind, randomised, controlled, clinical trials of oral triptans in migraine. We calculated summary estimates across studies for important efficacy and tolerability parameters, and separately summarised direct comparator trials.

Results 53 clinical trials (12 unpublished) involving 24 089 patients, met the criteria for inclusion. Mean results for 100 mg sumatriptan were 59% (95% CI 57–60) for 2 h headache response (improvement from moderate or severe to mild or no pain); 29% (27–30) for 2 h pain free (improvement to no pain); 20% (18–21) for sustained pain free (pain free by 2 h and no headache recurrence or use of rescue medication 2–24 h post dose); and 67% (63–70) for consistency (response in at least two of three treated attacks); placebo-subtracted proportions for patients with at least one adverse event (AE) were 13% (8–18), for at least one central nervous system AE 6% (3–9), and for at least one chest AE 1·9% (1·0–2·7). Compared with these data, 10 mg rizatriptan showed better efficacy and consistency, and similar tolerability; 80 mg eletriptan showed better efficacy, similar consistency, but lower tolerability; 12·5 mg almotriptan showed similar efficacy at 2 h but better other results; 2·5 mg naratriptan and 20 mg eletriptan showed lower efficacy and (the first two) better tolerability; 2·5 mg and 5 mg zolmitriptan, 40 mg eletriptan, and 5 mg rizatriptan showed very similar results. The results of the 22 trials that directly compared triptans show the same overall pattern. We received no data on frovatriptan, but publicly available data suggest lower efficacy.

Interpretation At marketed doses, all oral triptans were effective and well tolerated. 10 mg rizatriptan, 80 mg eletriptan, and 12·5 mg almotriptan provide the highest likelihood of consistent success.

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Introduction

Migraine is a common, chronic, multifactorial neurovascular disorder, typically characterised by recurrent disabling attacks of severe headache, autonomic nervous system dysfunction and, in up to a third of patients, neurological aura symptoms.[1,2] Ergot derivatives used to be the only specific treatments for migraine attacks, although they had many limitations.[3,4] Improved understanding of the neurobiology of migraine and 5-HT (5-hydroxytryptamine serotonin) receptors have resulted in a new class of selective 5-HT$_{1B/1D}$ agonists, known as the triptans.[5] They have three main mechanisms of action: cranial vasoconstriction, peripheral trigeminal inhibition, and inhibition of transmission through second order neurons of the trigeminocervical complex.[6] The relative importance of each of these mechanisms remains uncertain.[7,8] By contrast with ergots, triptans have selective pharmacology, simple and consistent pharmacokinetics, evidence-based prescribing instructions, well established efficacy, modest side-effects, and a well established safety record; they are, however, also contraindicated in the presence of cardiovascular disease.[9] Despite the higher price, triptans were preferred over ergots in most patients.[3,4]

Given that seven different triptans will soon be clinically available, physicians need evidence-based guidelines to select the triptans with the highest likelihood of success. Direct active comparator trials were available for only a few triptans and it is unlikely that they will ever all be compared. Although such studies were deemed the gold standard for comparing drugs, there were also some important caveats, complicating their interpretation.[10] The triptan trials were very similar in study methods and populations, facilitating meta-analysis to summarise the efficacy and tolerability of the different triptans across studies.[11,12] Previous triptan meta-analyses were based on summary data from published trials only, and only analysed a limited number of agents, doses, and outcome and adverse event variables.[13,14]

Although oral absorption of many drugs is delayed during migraine attacks,[15] most patients prefer oral formulations;[16] they account for more than 80% of all triptan prescriptions (H Mansbach, GlaxoSmithKline, personal communication). We shall therefore concentrate on the oral formulations. Sumatriptan is also available in parenteral formulations; these are discussed elsewhere.[10]

Methods

Clinical assessment in acute migraine trials

Typically, patients were instructed to treat a migraine headache when pain is moderate or severe on a 4-point pain severity scale (0=no pain; 1=mild; 2=moderate; 3=severe pain) and within 6–8 h of onset.[11] The primary endpoint in most studies was the proportion of patients with a headache response (ie, improvement to mild or no pain 2 h post-dose). More recently, the proportion of patients who become pain free 2 h post-dose has

become the preferred and clinically most relevant primary endpoint.[10,16,17] The headache may sometimes return within 24 h of initial relief (headache recurrence or relapse) requiring re-dosing.[1,18–20] This is inconvenient and may lead to medication overuse.[21,22] Simple comparison of recurrence rates (as proportion of responders) without accounting for differences in initial relief rates and use of rescue medications might be misleading.[1,10,23] We therefore recommend use of sustained pain-free: the proportion of patients who were pain free by 2 h post-dose and who do not have a recurrence of moderate or severe headache and who do not use any rescue headache medication 2–24 h post-dose.[1,10,23] It represents the ideal efficacy endpoint (ie, patients who require only a single dose to abort their attack by 2 h and for at least 24 h) but also the most difficult one to achieve.[16] Note that, with the definition used here, recurrence of only mild headache not prompting the use of rescue medication, will not be recorded; we, however, do not consider this a clinically significant recurrence. Patients also highly value a consistent effect over recurrent attacks (intrapatient consistency):[16,17] the proportion of patients with response (or painfree) in at least two or three of three actively treated attacks in placebo-controlled trials. Finally, tolerability and safety were mainly assessed by reporting of adverse events.

Meta-analysis of oral triptan trials

After a systematic review of published English trials, we sent a standard letter to all six pharmaceutical companies that market triptans. The letter explained the objectives and exact procedures of the study and asked for raw patient data of all randomised controlled trials (both published and unpublished) that used their drug. Five companies provided all the requested data. Vanguard (now Vernalis) declined to disclose any data on frovatriptan; data were thus extracted from congress abstracts. Where possible, we crosschecked all data with published or presented data. In addition, we approached the principal investigators of triptan trials that were not company-sponsored with the same request. The companies received the results (not the interpretations) of the analyses, for their drug only, 2 months before the planned submission of the manuscript, and were asked to check them for accuracy; there were no comments. The database was closed on Nov 1, 2000.

Studies and data included

Studies had to meet the following inclusion criteria: randomised, double-blind, controlled (placebo or active) clinical trial; treatment of moderate or severe migraine attacks within 8 h of onset in migraine patients (18–65 years of age) defined according to the International Headache Society criteria;[24] treatment with an oral triptan at a recommended clinical dose; and measurement of the headache on the 4-point pain scale.[11] We assessed in total 76 clinical trials: 53 met the eligibility criteria and 23 studies were excluded (see web tables 1 and 2 on *The Lancet's* website: www.thelancet.com); the most common reasons for exclusion were lack of a control group, use of non-recommended drug doses, or selected study populations (eg, adolescents).

We combined data from placebo-controlled trials, with or without an active comparator, in the meta-analysis (per patient, only the first study attack). Data from direct active comparator trials were also analysed separately. For rizatriptan, the results of both traditional tablets and soluble wafers were combined, as the study designs and results were identical.

Patients classified as having at least one adverse event (AE; any AE) typically had mild and short-lived tingling, paraesthesias, warm sensations in the head, neck, chest, and limbs, or less frequently, dizziness, flushing, and neck pain or stiffness. Central nervous system AE refers to the proportion of patients with at least one central nervous system AE (aesthenia, abnormal dreams, agitation, aphasia, ataxia, confusion, dizziness, somnolence, speech disorder, thinking abnormally, tremor, vertigo, and other focal neurological symptoms). Chest AE refers to the proportion of patients with at least one chest AE (chest pressure, chest pain, radiating pain in arm, other chest feelings, heavy arms, shortness of breath, palpitations, and anxiety).

Statistical analysis

We assessed differences in all endpoints between triptans and placebo with random effect models.[25] These models incorporate potential heterogeneity of the endpoints among different studies by assuming that each study estimates a unique endpoint.[26] We assessed the homogeneity of observed endpoints with the χ^2 test.[27] None of the endpoints showed homogeneity for all triptans. When between-studies variance is zero, the study is homogeneous for that triptan dose and endpoint; a random effect model is identical to a fixed effect model. Therefore, we used random effect models for all endpoints.

Although study design and eligibility criteria were remarkably similar across the triptan trials, even small differences may affect comparisons of treatment effects across studies. To control for these differences, at least partly, the placebo response may be subtracted from the active response (placebo-subtracted proportion or therapeutic gain). These metrics measure the incremental benefit of active drug over placebo; the implicit assumption is that these benefits were additive and the limitations recognised. Similarly, subtracting the placebo AE rate from the active drug AE rate can help to correct the differences in the methods of collection and definitions of AEs among studies (therapeutic harm). These approaches may facilitate across-trial comparisons[13] and have been used in other therapeutic areas including pain.[28] A similar outcome when using absolute proportions and when using placebo-subtracted proportions increases the validity of the results. We will therefore present data both ways. We also calculated the active drug:placebo ratios, another strategy to control for differences across studies, but will not show the data as these provided similar results.

Results

Sumatriptan is the first and most widely prescribed triptan: most European countries use 100 mg as the primary oral dose, whereas North America and some other countries use 50 mg.[10,29] We selected the 100 mg dose as the single reference dose for a number of reasons.[10]

Figure 1A shows the mean absolute and placebo-subtracted rates and 95% CI of the headache response at 2 h. Compared with 100 mg sumatriptan (mean 59% [95% CI 57–60]), 10 mg rizatriptan and 80 mg eletriptan showed higher, and 2·5 mg naratriptan, 20 mg eletriptan, and 2·5 mg frovatriptan (data from abstracts only) lower response rates. 2·5 mg

zolmitriptan had a slightly higher response rate than 100 mg sumatriptan ($p<0·05$), whereas the difference in rate for 50 mg sumatriptan, 5 mg zolmitriptan, and 5 mg rizatriptan was not significant. There were no differences for the other doses and drugs. Placebo-subtracted values showed wider CI and overlap between most triptans (mean for sumatriptan 100 mg=29% [95% CI 26–34]). A significant positive difference persisted for 80 mg eletriptan (42% [95% CI 36–48]) and a negative difference for 2·5 mg frovatriptan (17% [95% CI 13–20]).

Figure 1B shows the pain-free rates for each triptan. Compared with 100 mg sumatriptan (29% [95% CI 27–30]), 25 mg sumatriptan, 2·5 mg naratriptan, and 20 mg eletriptan showed lower mean absolute pain-free rates, whereas 80 mg eletriptan, 12·5 mg almotriptan, and 10 mg rizatriptan showed higher values. The other triptans and doses did not differ from 100 mg sumatriptan. Placebo-subtracted values (100 mg sumatriptan: 19% [95% CI 17–22]) were significantly higher for 10 mg rizatriptan and 80 mg eletriptan.

Compared with 100 mg sumatriptan (30% [95% CI 27–33]), recurrence rates were lower for 40 and 80 mg eletriptan and higher for 5 and 10 mg rizatriptan (figure 2A). 2·5 mg naratriptan had a lower recurrence rate, but this is based on 4 h rather than on 2 h response rates and is therefore not directly comparable. Other recurrence rates overlap. Isolated comparison of recurrence rates might be misleading so we have compared sustained pain-free rates (figure 2B). These were calculated, post-hoc, for those trials with all available relevant data. Compared with 100 mg sumatriptan (20% [95% CI 18–21]), sustained pain-free rates were higher for 10 mg rizatriptan, 80 mg eletriptan, and 12·5 mg almotriptan, and lower for 20 mg eletriptan. 25 mg sumatriptan and 2·5 mg naratriptan tended to show lower values, whereas no differences were reported for the other triptans. Because the interpretation of recurrence after a response following placebo is unclear no placebo-subtracted sustained pain-free rates have been calculated.

Placebo-controlled intrapatient consistency of efficacy over multiple attacks was investigated in only a few studies. No such studies were available for 25 and 50 mg sumatriptan, 2·5 and 5 mg zolmitriptan, and 5 mg rizatriptan. All drugs (except 10 mg rizatriptan) were tested in a parallel-group design, treating three consecutive attacks with either active drug or placebo (figure 3). These studies showed that consistent lack of response is rare: response in at least one of three treated attacks occurs in 79–89% of patients (placebo: about 50%) and freedom from pain in 51–59% (placebo: 18%). Response in at least two of three treated attacks occurs in 47–72% of patients (placebo: 17–33%) and freedom from pain in 14–42% (placebo: 3–13%); highest consistency rates were for 100 mg sumatriptan and 12·5 mg almotriptan (but here placebo rates were also highest); lowest rates were for 2·5 mg naratriptan and 25 mg sumatriptan. Response in all three attacks occurs in 16–47% of patients (placebo: up to 9%) and

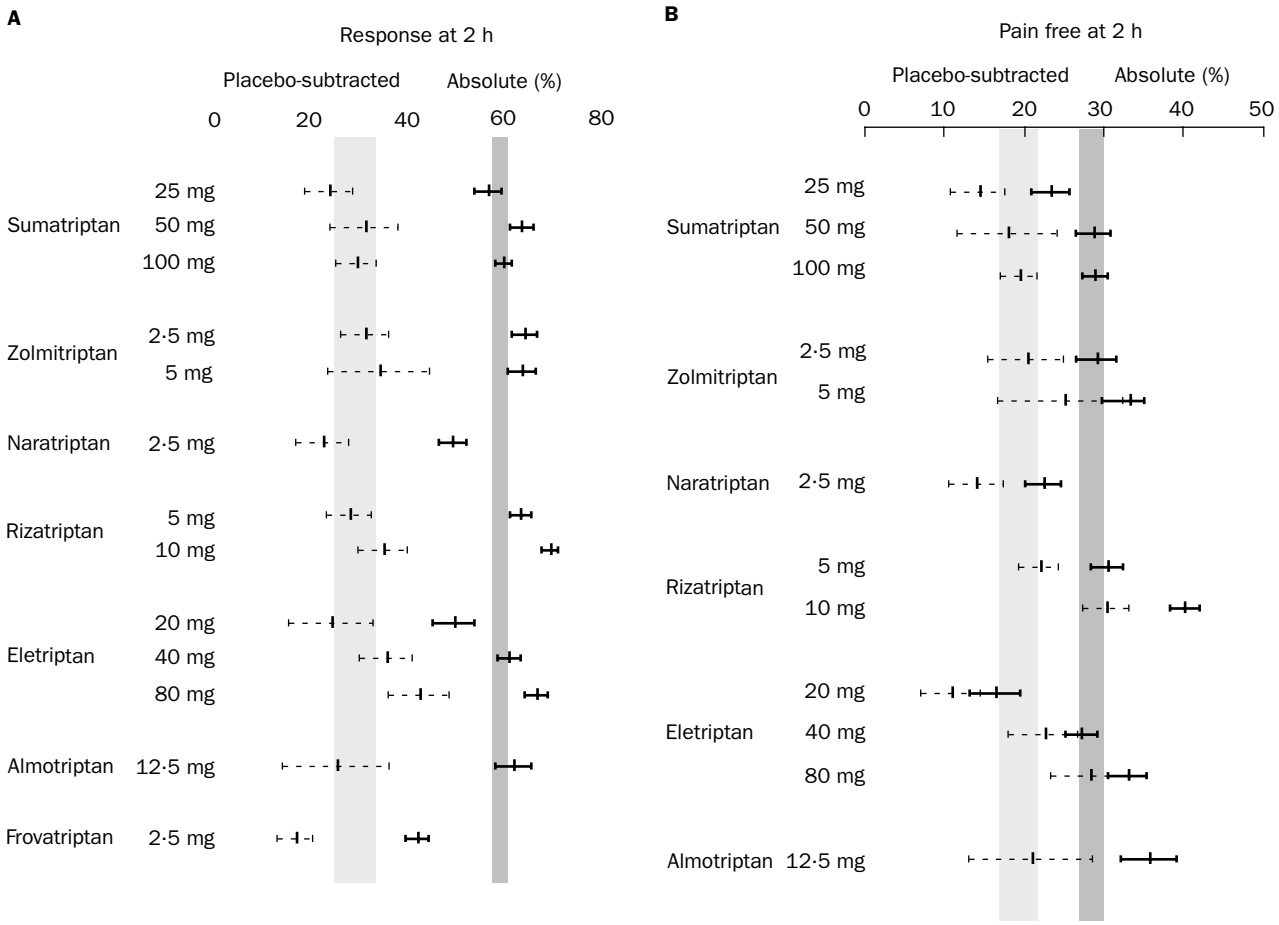

Figure 1: **Absolute and placebo subtracted efficacy results at 2 h**
A: rates of headache response; B: rates of pain-free. Mean and 95% CIs given for each triptan. Grey shaded regions are the 95% CIs for 100 mg sumatriptan.

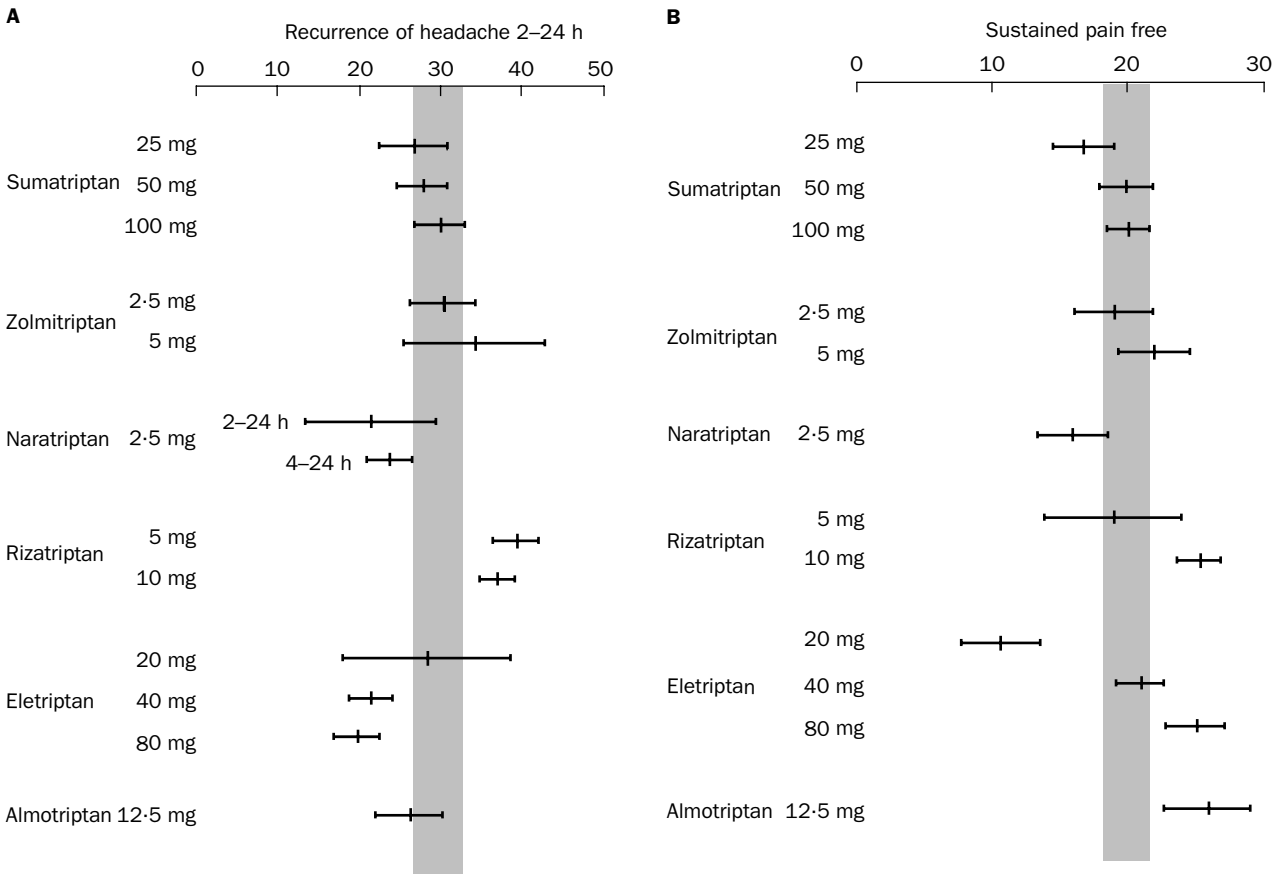

Figure 2: **Recurrence from 2–24h and sustained pain-free rate**
A: headache recurrence; B: sustained pain-free rates. Mean and 95% CI values given for each triptan. Grey shaded region is the 95% CI for 100 mg sumatriptan. For naratriptan the recurrence rate is given for 4–24 h post-dose (as presented in the original publications) and for 2–24 h post-dose (after recalculating the data).

freedom from pain in 1–17% (placebo: <2%); highest consistency rates were for 100 mg sumatriptan and 12·5 mg almotriptan (with highest placebo rates).

The consistency of 10 mg rizatriptan was assessed in a double-blind, crossover design over four attacks, with placebo in one attack interspersed at random in four of five patient groups; the fifth group received 10 mg rizatriptan for four attacks.[30] The different design of this study complicates a comparison with the other consistency rates, although it seems unlikely that it would have increased consistency. Consistency rates over three attacks were the highest of all triptans: response (and pain-free) rates were 96% (77%) in at least one of three, 86% (48%) in at least two of three and 60% (20%) in all three actively treated attacks.[31] In the subgroup of 125 patients who treated three consecutive attacks wih rizatriptan, without prior exposure to placebo, the results were very similar: response (and pain-free) rates were 87% (42%) in at least two of three attacks and 50% (16%) in all three attacks.

In figure 4 values greater than zero indicate that AE occurred in more patients for active drug than for placebo; values with narrow 95% CIs that cross the zero line indicate placebo-like incidences. 100 mg sumatriptan had a mean placebo-subtracted rate of any AEs of 13% (95% CI 8–18). Rates for other triptans overlap, except for lower values for 2·5 mg naratriptan and 12·5 mg almotriptan; these rates also do not differ from placebo. A similar pattern emerged when only AEs were included which were (blindly) considered by the trial investigator as drug-related (data not shown). For central nervous system AEs compared with 100 mg sumatriptan (6% [95% CI 3–9]), 80 mg eletriptan showed higher and 12·5 mg almotriptan lower values. For chest AEs compared with 100 mg sumatriptan (1·9% [95% CI 1·0–2·7]), 12·5 mg almotriptan showed a lower value. All other incidences overlap.

Comparison of the results for placebo and sumatriptan were discussed in detail elsewhere;[10] these data serve as internal standards to check for methodological differences among the studies conducted by the different companies. The placebo rates proved remarkably consistent across most companies except for very high efficacy and low AE rates in the almotriptan studies, and very low efficacy and high AE rates in the eletriptan studies. The sumatriptan efficacy rates were very consistent across companies except for low pain-free and sustained pain-free rates in the comparator studies versus eletriptan. The sumatriptan AE rates vary markedly; they were notably low in the comparator study versus almotriptan.

Webtable 3 summarises all 22 eligible trials that compared one triptan with another, or with ergotamine; they are reviewed in detail elsewhere.[10] The main efficacy and AE differences (and 95% CIs) between the two indicated compounds were listed; the primary study endpoints and appropriate statistics were indicated with grey boxes. Differences were generally small, which is to

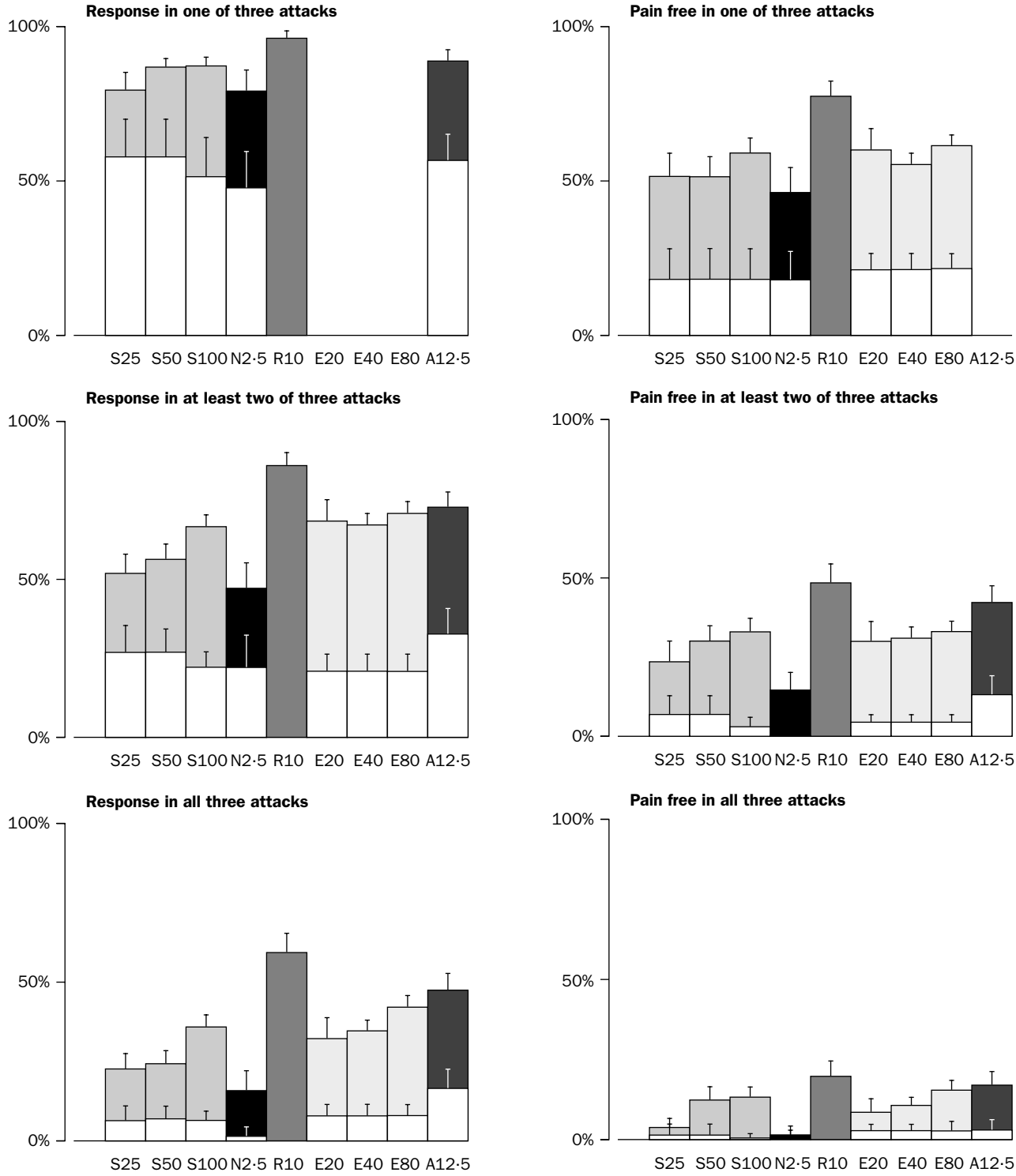

Figure 3: **Intra-individual consistency**
2 h headache response and pain free in at least one of three attacks, at least two of three, and all three attacks for each triptan. Data are presented as group result and 95% CI. For each drug the white bar indicates the consistency rate for placebo. For rizatriptan this could not be calculated due to the different design. S=sumatriptan. N=naratriptan. R=rizatriptan. E=eletriptan. A=almotriptan.

be expected when comparing active compounds, but the overall pattern is very similar to that in the meta-analysis.

Discussion

We used two complementary approaches for comparing the efficacy and tolerability of the oral triptans: a large meta-analysis of all the eligible, high-quality, randomised, placebo-controlled clinical trials and a separate analysis of all direct comparative studies. Both approaches give very similar results. Our meta-analysis used studies of a fundamentally similar design so that summary estimates of the efficacy and tolerability of the full range of compounds could be derived. The use of

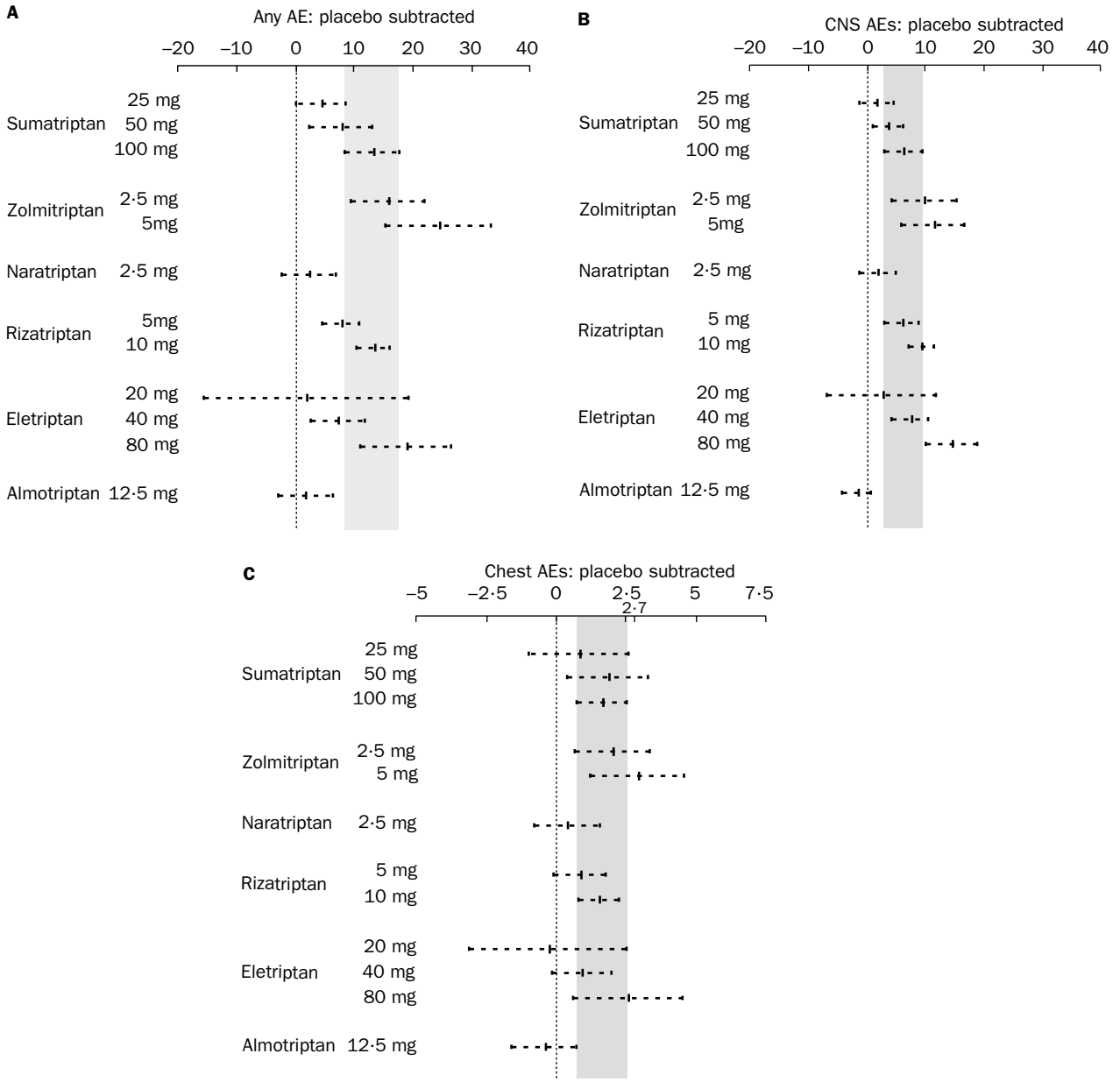

Figure 4: **Placebo subtracted AE data**
A: any AE, B: CNS AE, C: chest AE. Mean and 95% CI given for each triptan. Grey shaded region is the 95% CI for 100 mg sumatriptan.

placebo-subtracted measures allows partial adjustment for the methodological differences among studies that could affect the results. The great strength of randomised head-to-head comparator trials is their internal validity. However, factors such as patient selection, study size, and encapsulation of a drug may limit the generalisibility of the results into clinical practice.[10] Furthermore, it is unlikely that all triptans will ever all be compared. The remarkable similarity of the results from the meta-analysis of the placebo-controlled trials (both for the absolute and placebo-subtracted rates, and the active placebo ratios) and from the head-to-head studies drug: reinforces the validity of the conclusions.

Safety of drugs can only be reliably assessed after large-scale and long-term clinical exposure. Although less so than with the ergots,[3,4] the main concern with all triptans is their potential for coronary vasoconstriction.[32] This has been exacerbated by the occurrence of chest symptoms that sometimes resemble pectoral angina;[33] the usual underlying mechanism, however, is not myocardial ischaemia.[1,2] When patients were warned about these events, they rarely cause problems.[1,33] A recent long-term post-marketing review concluded that triptans were very safe as long as they were not used in patients with cardiovascular disease or major risk factors.[9] Since there were no clinically important differences in coronary vasoconstriction effects, no triptan is demonstrably safer than the others.

Differences in total AE rates must be interpreted cautiously since they reflect proportions of patients with at least one AE, irrespective of their number, nature, or intensity; trivial and significant AEs were thus pooled. In addition, in the almotriptan studies AE rates for placebo and sumatriptan are remarkably low. This finding could indicate different methods of collecting and defining AEs, a study population with a higher threshold for reporting AEs, or both.

All oral triptans were more effective than placebo.

	Initial 2 h relief	Sustained pain-free	Consistency	Tolerability
Sumatriptan 50 mg	=	=	=/–	=
Sumatriptan 25 mg	–	=/–	–	+
Zolmitriptan 2·5 mg	=	=	=	=
Zolmitriptan 5 mg	=	=	=	=
Naratriptan 2·5 mg	–	–	–	++
Rizatriptan 5 mg	=	=	=	=
Rizatriptan 10 mg	+	+	++	=
Eletriptan 20 mg	–	–	–	=
Eletriptan 40 mg	=/+	=/+	=	=
Eletriptan 80 mg	+(+)	+	=	–
Almotriptan 12·5 mg	=	+	+	++

Based on the results of the present meta-analysis and the direct comparator trials. =indicates no difference when compared with sumatriptan. + indicates better when compared with sumatriptan. – indicates inferior when compared with sumatriptan.

Comparison of the main efficacy and tolerability measures for the oral triptans versus 100 mg sumatriptan

Consistent lack of response is rare, as 79–89% of patients respond in at least one of three treated attacks. Differences among the triptans were small but were clinically relevant for the individual patient. Compared with 100 mg sumatriptan, 12·5 mg almotriptan was 24% better for pain-free, 30% better for sustained pain-free, and 57% for adverse events. 80 mg eletriptan was 10% better for response and 25% better for sustained pain-free, whereas 10 mg rizatriptan was 17% better for response, 38% better for pain-free, and 25% better for sustained pain-free. When including consistency over all three attacks, the percentages for rizatriptan were even higher (67% for response and 58% for pain-free).

The table above compares the main efficacy and tolerability measures for the oral triptans versus sumatriptan. Three compounds showed favourable results: 10 mg rizatriptan, 80 mg eletriptan, and 12·5 mg almotriptan. In the almotriptan trials, placebo efficacy was high and AE rates for placebo and sumatriptan were very low. This suggests that the patients in these studies were more therapy-responsive and had a higher threshold to report AEs; however, almotriptan retained its tolerability advantage in a head-to-head study with 100 mg sumatriptan (webtable 3). In the direct comparator trials versus eletriptan, sumatriptan (but not eletriptan) was encapsulated (for masking purposes) and significantly underperformed for freedom from pain compared with other trials. In a pharmacokinetic study, the early absorption of encapsulated sumatriptan was delayed compared with that of normal sumatriptan, but the open label 2 h responses were equivalent.[34] For the other compounds, differences were minor and sometimes favour 100 mg sumatriptan. 50 mg sumatriptan, 2·5 mg and 5 mg zolmitriptan, 5 mg rizatriptan, and 40 mg eletriptan have efficacy and tolerability profiles very similar to 100 mg sumatriptan. 25 mg sumatriptan, 2·5 mg naratriptan, and 20 mg eletriptan have inferior efficacy, but better tolerability.

Data for frovatriptan were not received nor published. Based on congress abstracts, headache response (41%; placebo 21%) and pain free (12%; placebo 3%) were well below those of the other triptans. Recurrence and AE rates do not significantly differ from 100 mg sumatriptan; therefore, a claim for better cardiovascular safety is unsustainable and potentially hazardous.[10]

Patients' characteristics and preferences vary, and individual responses to a triptan cannot be predicted. Finding the best therapy may involve trial and error: if the first triptan fails one may successfully switch to another. Physicians thus need more than one triptan in their repertoire to best treat patients with migraine. 10 mg rizatriptan (especially when consistent and rapid freedom from pain is desired), 80 mg eletriptan (especially when high efficacy and low recurrence were favoured over tolerability), and 12·5 mg almotriptan (especially when high tolerability and good efficacy were favoured) offer the highest likelihood of success. 100 mg and 50 mg sumatriptan provide good efficacy and tolerability and by far the longest clinical experience. Sumatriptan also, and uniquely, offers non-oral formulations, allowing tailor-made treatments; the 6 mg subcutaneous formulation is the most effective acute migraine treatment, but is also associated with more intense AEs and the need for self-injection.[35] 2·5 mg naratriptan offers very good tolerability coupled to a slower onset of improvement; this can be useful in patients with mild or moderate migraine. 2·5 mg and 5 mg zolmitriptan were good alternatives in many patients; they offer no specific advantages nor flaws. Frovatriptan cannot be fully judged in view of the lack of data but does not seem to offer any particular advantage.

Contributors

M D Ferrari initiated, coordinated, and supervised the study, and helped in designing the meta-analysis, data analysis, interpretation of the results, and writing the paper. K I Roon coordinated the contacts with the principal investigators of the trials and the manufacturers of the seven triptans, collected raw patient data, and checked the validity of the data. She did the primary data analyses and statistics, contributed to data interpretation, and the writing of the paper. R B Lipton and P J Goadsby contributed to designing the meta-analysis, data analysis, interpretation of the results, and writing of the paper.

Conflict-of-interest statement

M D Ferrari's salary is fully covered by LUMC. He has received: consultancy and industry support from Allergan, Almirall, AstraZeneca, Boehringer, Glaxo Wellcome, Merck, Sharpe & Dohme, Pfizer, SmithKlineBeecham,Vanguard Medica; grant support from Glaxo Wellcome, Merck, Sharpe & Dohme; and independent support from NWO, Asclepiade, Migraine Trust, Dutch Brain Trust, Biomed EC, Dutch Heart Foundation, and the Gisela Thier Foundation.
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