A triptan too far?

The past decade has seen a remarkable transition in neurological practice which has been driven in considerable measure by therapeutic developments. Clinical neurology, once driven primarily by the diagnostic process, is increasingly becoming a therapeutic speciality. Headache, so often the ugly sister, ubiquitous, ill-understood, and ever bothersome in the clinic, has given up some of its secrets to enrich our practice and improve the life of our patients. For headache treatment the 1990s will be the decade of the triptans: 3,5 substituted indole, selective serotonin (5HT1B/1D) agonists, sumatriptan and its relatives. As the second generation of the triptans emerge this editorial attempts to provide a summary of the new compounds and formulations which will be a basis for defining the new medicines' place in clinical practice. I will start with the question of whether there is a need for newer treatments, outline the methods used for the clinical assessments, and conclude by suggesting some of the situations in which any or some of the new drugs have an advantage.

To be practical I will consider the triptans that are actually available now in many parts of the world, particularly in Europe. As decisions to use these compounds are now faced daily by both neurologists and general practitioners this review will focus on sumatriptan, naratriptan, and zolmitriptan. Other compounds, including rizatriptan, which has completed phase III development and which should appear next, and eletriptan, which is currently in late phase III, as well as drugs less well known and still in development, such as VML251 and almotriptan, will not be considered because they are not currently available. The principles used to review the available compounds could be applied to newer compounds when they become available.

Do we need new treatments for acute migraine attacks?

Before the introduction of sumatriptan in the early part of this decade patients managed with simple analgesics, such as aspirin or non-steroidal anti-inflammatory drugs (NSAIDs), coupled with antiemetics, or preparations containing ergotamine. Many patients did well but many did not. Sumatriptan was developed to mimic the effects of serotonin (5HT1B/1D) and to some extent was a refinement of ergotamine in a pharmacological sense. Given the side effect problems of ergotamine the emergence of sumatriptan was not surprising, although complete ergotophobia is perhaps more a marketing tool for triptans than a clinical imperative. Certainly, dihydroergotamine, an analogue of ergotamine, has much less prominent arterial vasoconstrictor effects, and can be a useful drug, particularly in the clinical setting in which headache recurrence is a major problem. The intranasal formulation of dihydroergotamine is certainly efficacious although less rapidly acting than sumatriptan. Intravenous dihydroergotamine is useful in the management of patients with intractable headache and is perhaps underused in that setting. Given the relatively good efficacy of aspirin and antiemetic combinations, what improvements are desirable?

After the initial development of sumatriptan the areas where further drug development would be useful surround oral therapy and alternative formulations. New treatments should attempt to maximise oral efficacy, provide rapidly acting oral medications, offer good response consistency within patients from attack to attack, prevent the development of headache recurrence, and minimise side effects from treatment. Furthermore, as some patients' attacks will not be well treated by oral medications choice in delivery formulations is an important development aim. It is fair to say that sumatriptan has fast become perceived by the pharmaceutical industry, and by many practitioners, as the gold standard treatment for acute migraine and this perception is reflected in the fact that all major triptan development programmes have built in sumatriptan comparisons. Given that the holy grail, as driven by perceptions of what patients would prefer, is the best possible oral medication, where do we turn?

Methods of assessing clinical trials in migraine

Although this is not the place to explore in detail the many issues surrounding clinical trials in migraine some of the issues require explanation to place in context the results of the new drugs. To some extent the limitations of sumatriptan have been obscured by the use of headache response as the primary end point in migraine clinical trials. In most acute migraine studies patients treat pain which is either of moderate or severe intensity and a response is defined as the proportion of patients with a moderate or severe headache who have mild or no headache (grade 2 or 3 becomes 1 or 0) at some specified time point, usually two or four hours after drug administration. It has proved very useful in research studies but has the distinct problem of overestimating effects because the one point transition from moderate to mild headache counts as a response. For this review both headache response and headache free (proportion of patients with no headache) data will be quoted and only for the two hour time points. The natural history of a migraine attack is to stop so that the use of the four hour time point has led to flatteringly high headache response data, which translate into unrealistic expectations for clinicians and disappointment for patients.

The International Headache Society Migraine Clinical Trials Committee recommends the use of headache free as the primary end point in acute attack studies (P. Ffelt-Hansen (chairman), personal communication). It has the virtue of simplicity, is intuitive to consumers, doctors, and patients alike, and whereas patients may differ in their definition of mild headache absence of pain seems quite clear. Unfortunately until sufficient data for all compounds are published on the pain free end point so the headache response end point must be used to compare and contrast emerging treatments and formulations. The use of 95% confidence intervals (95% CIs) will tell practitioners the likely range of the true headache response and thus more clearly present what is to be expected when a drug is used. Practitioners must also consider the placebo responses in assessing the results of clinical trials.
particular when comparing different drugs as placebo response rates sometimes vary widely from study to study. This can be done by comparing the therapeutic gain (response on active drug minus response to placebo) as a percentage and assumes that the benefit of the active drug is added to that of placebo. The calculation effectively nets out the placebo responses. The different but parallel consideration of the headache response and the therapeutic gain represents, to some extent, the jump all practitioners must make between clinical practice and clinical science. Both have a valid and important role in what must ultimately be the pragmatic decisions of everyday clinical work.

An alternative concept is the number needed to treat (NNT). The NNT is the reciprocal of the therapeutic gain when expressed as a proportion. As an example, if there is a 60% response to an active drug and a 25% placebo response the therapeutic gain is 35%, or as a proportion 0.35 with the NNT being 1/0.35 or 2.86. The number indicates that on average 2.86 patients would need to treat one attack to get one response truly due to the drug. Thus smaller NNTs are better. A similar concept may be calculated from adverse events and termed NNH (number needed to harm) in which bigger numbers are better. For the analyses presented data are derived from published and abstracted sources as cited and combine

### Practical implications of methods of assessing trials

Response rates at two hours, be they headache response or headache free, summarise the outcome from a clinical trial (fig 1). This is the effect that will be seen in practice as the placebo effect will be included in normal clinical settings. The therapeutic gain corrects for the effect of placebo (fig 2) and allows some initial comparisons of compounds, tempered by the knowledge that the only rigorous comparison is a specifically designed comparative trial. Despite this caveat, therapeutic gain removes the differences in placebo response rates, which have varied widely in many studies. The use of placebo correction is an imperfect way to compare different study programmes but, without well conducted and clear comparative studies, at least provides the clinician with some guides as to what to expect of a new drug when considered against the compounds that have been used. The use of NNT comparisons will no doubt increase and may become linked to cost estimations as questions of drug value become more important.

### Sumatriptan

Sumatriptan is relatively poorly absorbed with an oral bioavailability of 14% and a $T_{\text{max}}$ of 2–2.5 hours (table 2). It is metabolised via monoamine oxidase leading to the theoretical possibility of the serotonin syndrome. This is not a major issue in practice but does cause concern in a small group of patients as MAO inhibitors are useful prophylactic agents in migraine. Based on a meta-analysis of all the sumatriptan clinical studies that have been published, containing more than 3000 patients, the headache response (3/2≥1/0) was 56% (95% CI 51%–61%) for 50 mg and 58% (95% CI 56%–601%) for 100 mg, whereas the therapeutic gain for the headache response was 33% (95% CI 25%–40%) for the 50 mg tablets and 33% (95% CI 29%–36%) for 100 mg (P Tfelt-Hansen, personal communication). Similar overall summary data for the headache free end point are not currently available but in a large placebo controlled multicentre study with nearly 1000 patients the headache free rate was 31% (95% CI 26%–36%) for 50 mg and 35% (95% CI 29%–41%) for 100 mg with the corresponding headache free therapeutic gain being 22% (95% CI 14%–30%) and 26% (95% CI 18%–32%) respectively for 50 mg and 100 mg tablets. Headache recurrence is seen in about 30%-35% of patients and was not adequately recognised as a problem until the very carefully conducted sumatriptan studies characterised it. For the relief that the patient obtains there is a price in side effects and these have been recorded as adverse events in the placebo controlled studies. Because of the nature of the

### Table 1: NNT* data for currently available triptans

<table>
<thead>
<tr>
<th>Compound</th>
<th>NNT</th>
<th>NNH†</th>
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<tbody>
<tr>
<td>Sumatriptan</td>
<td>3.0</td>
<td>14.3</td>
</tr>
<tr>
<td>Naratriptan</td>
<td>4.8</td>
<td>1181 (24–)‡</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>2.9</td>
<td>5.9</td>
</tr>
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* NNT=number needed to treat. † NNH=number needed to harm. ‡ 95% CI.

**Figure 1** Comparison of headache responses (moderate or severe pain becomes mild or absent) at two hours postdose for each of sumatriptan, naratriptan, and zolmitriptan with the headache response (severe/moderate becomes nil or mild) at two hours on the ordinate. Each drug with corresponding currently used doses are listed on the abscissa and the data are the 95% CI. The horizontal dashed line provides the 95% CI for sumatriptan 100 mg which, as the first and most widely used drug of the class, provides a reference.

**Figure 2** Therapeutic gain at two hours for selected triptans at commonly used doses. Therapeutic gain defined as headache response (moderate/severe becomes nil/mild) at two hours minus headache response to placebo are included for sumatriptan, naratriptan, and zolmitriptan. Data are given as 95% CIs and the horizontal dashed line provides the 95% CI for sumatriptan 100 mg which, as the first and most widely used drug of the class, provides a reference.
Assembled from published data. 20, 29–31, 40–42, 44

*Measure of lipophilicity.

It has a longer T1/2 but paradoxically, and sumatriptan at 63%-74%, for male and female patients excretion and metabolism in the liver through Naratriptan, similar to sumatriptan, is a 5HT1B/1D agonist. Naratriptan 100mg (fig 3).25

That on placebo) for sumatriptan are a mean of 7% (95% CI 64–84%) for 50 mg and 17% (95% CI 20–26%) for 100 mg (fig 3).25

The therapeutic penalty data (adverse event on active drug minus adverse event rate on placebo) from all causality adverse event data plotted on the ordinate. Data are given as 95% CI and the horizontal dashed line provides the upper 95% CI for sumatriptan 100 mg which, as the first and most widely used drug of the class, provides a reference.

Figure 3 Therapeutic penalty for each of the compounds reviewed. Comparison of adverse event rates expressed as therapeutic penalty (adverse event on active drug minus adverse event rate on placebo) from all causality adverse event data plotted on the ordinate. Data are given as 95% CI and the horizontal dashed line provides the upper 95% CI for sumatriptan 100 mg which, as the first and most widely used drug of the class, provides a reference.

reporting system, which is all inclusive, there are more adverse events than true side effects and the terms are not interchangeable. The adverse event rate is relatively comparable between drugs as broadly similar “everything is recorded” systems are used by industry. However, some variation can develop according to whether adverse events are recorded prospectively in a diary, recorded at follow up, or even probed for by knowledgeable investigators. The therapeutic penalty data (adverse events on active minus that on placebo) for sumatriptan are a mean of 7% (95% CI 0%-14%) for 50 mg and 17% (95% CI 10%-24%) for 100 mg (fig 3).25

Naratriptan
Naratriptan, similar to sumatriptan, is a 5HT1B/1D agonist. Its basic pharmacological profile is the same as that of sumatriptan with the exception of increased lipophilicity (table 2). It is active in models used to select antimigraine activity.27, 28 Naratriptan has better bioavailability than sumatriptan at 63%-74%, for male and female patients respectively.29 It has a longer T1/2 but paradoxically, and without current explanation, a longer Tmax at 2.5–3 hours.30 Unlike sumatriptan its main route of elimination is by renal excretion and metabolism in the liver through P-450 enzyme systems31 meaning that there is no interaction with MAO inhibitors. Naratriptan was characterised through a 100-fold dose range from 0.1 mg to 10 mg and deliberately developed to target clinical shortcomings associated with sumatriptan in particular, to improve tolerability and reduce recurrence of headache. The headache response based on a meta-analysis of the phase II/III clinical trial programme for naratriptan was 48% (95% CI 45%-51%) at two hours with a therapeutic gain of 21% (95% CI 18%-24%) and for the headache free end point 23% (95% CI 20%-26%) with a corresponding therapeutic gain of 15% (95% CI 12%-18%) for the recommended clinical dose of 2.5 mg.

Formal data for consistency of the headache response within a patient show that 73% of patients respond on two out of three attacks compared with 75% for sumatriptan 100 mg and 22% for placebo. These are, however, four hour data and no data for the two hour time point are currently available. As an aside consistency as a term should probably be restricted to indicate within patient consistency rather than the less meaningful concept of population responses on sequential attacks. Naratriptan has a slower onset of action than sumatriptan but has a lower rate of headache recurrence.32 It is important to note, given that headache recurrence has not been defined consistently across the triptan studies, that historical controls and comparisons are probably of little value and claims for a benefit in terms of headache recurrence are best based on head to head blinded studies, such as this one and those done for dihydroergotamine.33, 34 As with sumatriptan35 blinded studies have failed to show efficacy for naratriptan in the adolescent population.36 Naratriptan at 2.5 mg is better tolerated than sumatriptan with an adverse event rate across all the studies, corrected for placebo, of 0.1% (95% CI 4–2.4%). It should be noted that the 95% CI crosses zero and that the incidence of adverse events at this dose in the controlled studies was very low.

Zolmitriptan
Zolmitriptan was the second of the 5HT1B, class to be marketed in the United Kingdom after sumatriptan and was designed to be more lipophilic37 and to be a potent partial agonist.38 Both aims were achieved and its activity in preclinical models is well established as it has been used as a laboratory tool for considering some issues surrounding the potential central sites of action of this class of compounds.39–41 It has a T1/2 of three hours42 and a Tmax of one hour43 with an oral bioavailability of 40%.44 It is also metabolised through the P-450 system and has an active metabolite (N-desmethyl-zolmitriptan) which is a 5HT1D agonist that is two to six times more potent than the parent compound.45 The active metabolite has the same plasma concentration-time profile and is likely to contribute to the therapeutic effects of the parent compound. The N-desmethyl metabolite is degraded by MAO-A (table 2). This does not create a clinically significant effect on initial dosing but does limit the total dose to 5 mg per day with concomitant MAO inhibitor therapy. There is an increase in the Cmax of zolmitriptan (10 mg) of 37% with propranolol coadministration (160 mg/day)46 accompanied by a reduction in the N-desmethyl metabolite of 24%47 which again again does not limit use of the 5 mg dose. It is not clear whether this effects due to inhibition of P-450 enzymes48 or due to reduced hepatic blood flow.49 Based on a meta-analysis of the phase II/III placebo controlled studies zolmitriptan has, at two hours, a headache response of 64% (95% CI 59–69%) with a therapeutic gain of 34% (95% CI 27–41%) for 2.5 mg, and a headache response of 66% (95% CI 62–70%) with a corresponding therapeutic gain of 37% (30–44%) for the 5 mg dose.50 For comparison the headache free end point at two hours was 25% (95% CI 21–29%) with a therapeutic gain of 19% (14–24%) and 34% (95% CI 30–38%) with a therapeutic gain of 28% (23–33%), for the 2.5 mg and 5 mg doses, respectively.

Given the corresponding adverse event rates, the therapeutic penalty rates are 17% (95% CI 11–23%) and 29% (95% CI 23–35%), for 2.5 mg and 5 mg, respectively.

On this basis the recommended starting dose of 2.5 mg provides the best balance of benefit and side effects
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I think not. As a general comment it should be noted that response rates in clinical practice are usually somewhat higher than in controlled studies, which is a bonus for practitioners and patients. Each of the additions to treatment thus far have brought a particular utility while supplying some interesting questions. The sumatriptan nasal spray is a helpful adjunct\(^2\) that finds particular use with a more rapid onset of action than oral sumatriptan\(^1\) and the benefit for some patients of not having to resort to an injection. If one is thinking of the sumatriptan injection then the spray should at least be considered and if headache recurrence is an additional issue, the combined clinical problem should lead to the consideration of the dihydroergotamine spray, which can be obtained easily in Europe and is about to be released in the United States. Naratriptan at 2.5 mg is an ideal drug in patients sensitive to side effects or in whom headache recurrence on sumatriptan is an important issue. It would not be a wise choice if speed of onset were an important consideration or if they had already failed to respond to sumatriptan. Zolmitriptan is a very useful addition to the therapeutic armamentarium of migraine, although this has not been adequately used in clinical practice. It would not be a wise choice if they had already failed to respond to sumatriptan. Zolmitriptan is an important issue. It would not be a wise choice if speed of onset were an important consideration or if they had already failed to respond to sumatriptan. Zolmitriptan is an important issue. It would not be a wise choice if speed of onset were an important consideration or if they had already failed to respond to sumatriptan. Zolmitriptan is an important issue. It would not be a wise choice if speed of onset were an important consideration or if they had already failed to respond to sumatriptan. Zolmitriptan is an important issue.

In all the arguments that will ensue as clinical trial data are assimilated into routine practice we must emphasise the principle of fitting the treatment or formulation to the patient, individualising care, not trying to insist that all patients fit into one treatment. We must seek consistent, well tolerated, and safe treatment, although this has been successfully tested, with rapid onset of action and good tolerability. Although I would not stop a patient who is safely and successfully using sumatriptan and change them to zolmitriptan, if efficacy or speed are issues and the patient wants to examine other options, it would be the obvious first step which may obviate the need for a nasal spray or injection.

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