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Clinical effectiveness of migraine therapy: the number needed to treat and therapeutic gain methods

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Introduction

The evaluation of new medicines for headache is an important issue from several perspectives. The evaluation of new medicines with regard to pharmaco-economic benefit is explicitly covered in Chapter 8; in this chapter I will address some of the various methods currently used to assess compounds against placebo and then between each other. The issues will be illustrated by the triptan class of drugs (Goadsby 1998a), which are used in the acute treatment of migraine (Lance & Goadsby 1998). The review is divided into a discussion of endpoint measures and then a consideration of some summary measures – the therapeutic gain and number needed to treat (NNT).

Endpoints in migraine clinical trials

The issue of which endpoints to use is somewhat vexed. Some options are listed in Table 7.1. The list is not exhaustive but illustrates the problem. In essence, there is a competition between the need for scientific rigour, particularly in establishing efficacy in a new class of medicines – the core problem that faced the sumatriptan development team – and the need to provide clinically useful information, which is a more pressing need as the triptan class is more clearly established. To some extent this conflict remains one of the great challenges for the next century.

The International Headache Society Committee on Clinical Trials in Migraine is currently recommending that the primary efficacy outcome should be headache-free at 2 hours. Although more rigid definitions have been recommended by the Committee for several years (The International Headache Society Clinical Trials Committee in Migraine 1991), the most commonly used definition for the primary endpoint has been the headache response or headache relief endpoint in which the patient treats an attack in the study only if they have a moderate or severe headache that is not improving. A patient is considered a responder if at 2 or 4 hours they have nil or mild headache (Goadsby *et al.* 1991). The sumatriptan clinical trial programme used this endpoint (Pilgrim 1991) and this has driven competitors to use similar outcome measures. Several issues arise, including the appropriate time (2 or 4 hours), the comparative value of the headache-free endpoint and the reporting of the outcomes from the trials.

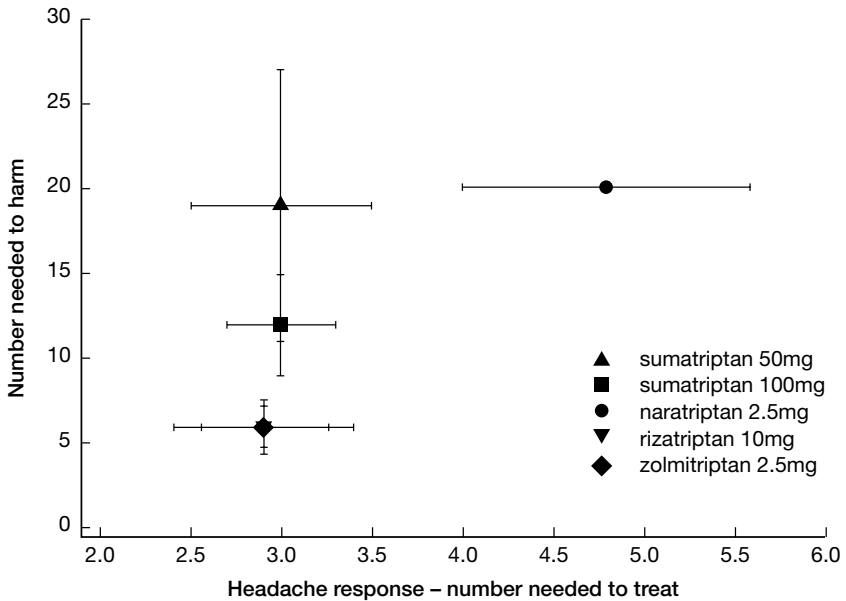


Figure 7.6 Comparison of number needed to treat (NNT) and number needed to harm (NNH) for the triptans. This analysis suggests they are very similar in both dimensions with only naratriptan being demonstrably different. There is no confidence interval for naratriptan adverse events (NNH) because the difference is so small from placebo rendering the calculations less useful

and suggests there may actually be no difference between them. NNT calculations have been used as crude measures of cost per effective treatment by multiplying by the dose cost but again, without confidence intervals, this calculation is almost completely meaningless and indeed may be deceptive.

Conclusions

The study of migraine in clinical trials has come a long way in the last decade with the standardisation of patient groups and some very considerable similarities in entry and endpoint measurements across development programmes for new medicines. Unfortunately, the endpoints we use are somewhat crude. Migraine is much more than headache so that by measuring headache relief as an endpoint there is much about the new treatments that is not captured. The challenge for the future is to understand the benefits, and the disadvantages, of the current treatments from the patient's perspective so that we can tease out important differences between treatments and thus design studies and ultimately make evidence-based decisions when selecting treatments for acute migraine.

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References

- Armitage P & Berry G (1994). *Statistical methods in medical research* 3rd edn. Blackwell Science, Oxford.
- Davies GM, Santanello NC, Kramer M, Matzura-Wolfe D & Lipton RB (1998). Determinants of patient satisfaction with migraine treatment. *Headache* **38**, 380.
- Dahlof C, Diener HC, Goadsby PJ *et al.* (1998). Zolmitriptan, a 5HT_{1B/1D} receptor agonist for the acute oral treatment of migraine: a multicentre, dose-range finding study. *European Journal of Neurology* **5**, 535–43.
- Goadsby PJ (1997a). Current concepts of the pathophysiology of migraine. In *Neurologic clinics of North America* Vol.15 (ed. NT Mathew), pp.27–41. WB Saunders, Philadelphia.
- Goadsby PJ (1997b). Naratriptan in the treatment of acute migraine attacks. *Prescriber* **8**, 89–97.
- Goadsby PJ (1998a). 5HT_{1B/1D} agonists in migraine: comparative pharmacology and its therapeutic implications. *CNS Drugs* **10**, 271–86.
- Goadsby PJ (1998b). A triptan too far. *J Neurol Neurosurg Psychiatry* **64**, 143–7.
- Goadsby PJ (1999). Rizatriptan in the treatment of acute migraine attacks. *Prescriber* **10** (in press).
- Goadsby PJ, Zagami AS, Donnan GA *et al.* (1991). A double blind placebo controlled crossover study of sumatriptan in the treatment of acute migraine attacks. *Lancet* **338**, 782–3.
- Grof P, Joffe R, Kennedy S, Persad E, Syrotiuk J & Bradford D (1993). An open study of oral flesinoxan, a 5-HT_{1A} receptor agonist, in treatment-resistant depression. *International Clinical Psychopharmacology* **8**(3), 167–72.
- The International Headache Society Committee on Clinical Trials in Migraine (1991). Guidelines for controlled trials of drugs in migraine. *Cephalalgia* **11**, 1–12.
- Jhee SS, Salazar DE, Ford NF, Fulmor IE, Sramek JJ & Cutler NR (1998). Monitoring of acute migraine attacks: placebo response and safety data. *Headache* **38**, 35–8.
- Kalbfleisch JD & Prentice RL (1973). Marginal likelihoods based on Cox's regression and life model. *Biometrika* **60**, 267–78.
- Kramer MS, Matzura-Wolfe D, Polis A *et al.* (1998). A placebo-controlled crossover study of rizatriptan in the treatment of multiple migraine attacks. *Neurology* **51**, 773–81.
- Lance JW & Goadsby PJ (1998). *Mechanism and management of headache* 6th edn. Butterworth-Heinemann, London.
- MaassenVanDenBrink A, Reekers M, Bax WA, Ferrari MD & Saxena PR (1998). Coronary side-effect potential of current and prospective antimigraine drugs. *Circulation* **98**, 25–30.
- The Multinational Oral Sumatriptan and Cafergot Study Group (1991). A randomized, double-blind comparison of sumatriptan and cafergot in the acute treatment of migraine. *Eur Neurol* **31**, 314–22.
- NewmanTancredi A, Gavaudan S, Conte C *et al.* (1998). Agonist and antagonist actions of antipsychotic agents at 5-HT_{1A} receptors: a [S-35]GTP gamma S binding study. *Eur J Pharmacol* **355**(2–3), 245–56.
- Pfaffenrath V, Cunin G, Sjonell G & Prendergast S (1998). Efficacy and safety of sumatriptan tablets (25 mg, 50 mg, and 100 mg) in the acute treatment of migraine; defining the optimum doses of oral sumatriptan. *Headache* **38**, 184–90.
- Pilgrim AJ (1991). Methodology of clinical trials of sumatriptan in migraine and cluster headache. *Eur Neurol* **31**, 295–9.