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Understanding the evidence from clinical studies on migraine

Introduction

Physicians are regularly bombarded with evidence from new publications in their specialty areas, which they have to integrate into their everyday practices. This can be a confusing business, as the quality of evidence varies from paper to paper. The challenge is to sift out the high-quality evidence that influences practice from the lower-quality evidence that does not. This is the science of evidence-based medicine that we are encouraged to practice.

This MIPCA (www.mipca.org.uk) newsletter provides advice on how to evaluate evidence from published clinical studies and reviews, concentrating on the acute treatment of migraine. We discuss how to distinguish high-quality from lower-quality evidence, and illustrate this with clinical data on the triptans. Finally, we present a new outcome tool for migraine, the Migraine Assessment of Current Therapy (Migraine-ACT) questionnaire, which is a simple means of evaluating the success of therapy. The newsletter is based on discussions and debate from a recent MIPCA meeting.[1]

Evaluating evidence from clinical studies

We now have clear published guidelines for the evaluation of clinical studies,[2] which are illustrated in Table 1.

Grade	Clinical recommendation	Level of evidence	
A	Essential in order to make clear recommendations for clinical practice	Ia:	systematic meta-analyses of controlled clinical studies
		Ib:	one or more randomised clinical studies
B	Does not influence practice. Can only be used to guide the objectives and design of future clinical studies	IIa, IIb:	well-designed non-randomised studies
		III:	descriptive studies, e.g. case studies
C	Does not influence practice. Can only be used to guide the objectives and design of future clinical studies	IV:	clinical judgement in the absence of objective evidence, e.g. expert committee reports

Table 1. Evidence-based medicine: grades of clinical evidence.[2]

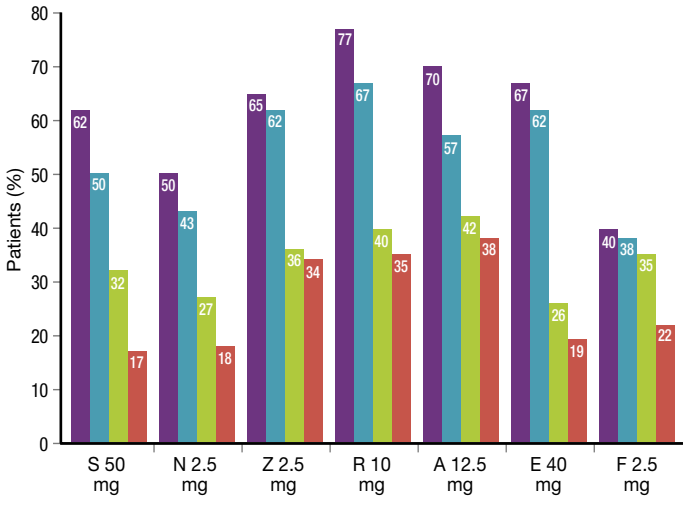
Only Grade A evidence can be used to influence clinical practice. Grade B and C evidence can only be used to guide the development of future clinical studies.

We provide expanded guidelines on how to evaluate data from individual studies and other sources on pages 2 and 3.

Evaluating the triptans

Clinical evidence on the triptans is of universally high quality, with multiple Grade A clinical studies conducted for all seven drugs currently licensed. Figure 1 shows a summary of the data obtained from placebo-controlled studies with the oral triptans.[1]

Figure 1. A summary of data from Grade A placebo-controlled studies with the oral triptans: proportions of patients improving from severe or moderate headache to mild or no headache at 2 hours after treatment.[1] (S = sumatriptan; N = naratriptan; Z = zolmitriptan; R = rizatriptan; A = almotriptan; E = eletriptan; F = frovatriptan)



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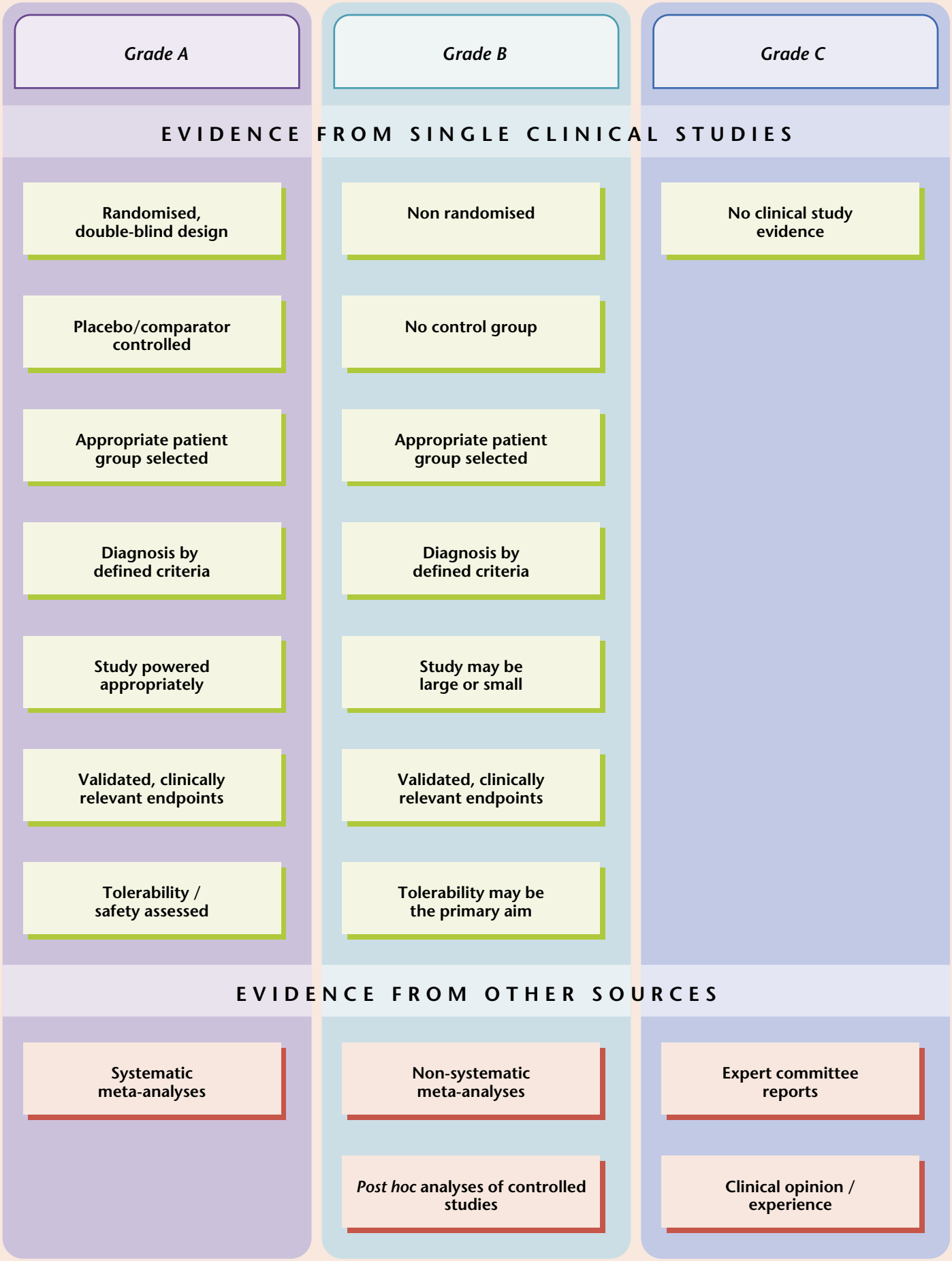

Figure 2. How to evaluate evidence from clinical studies.

Here, we provide advice on how to rate the quality of clinical studies. While migraine is used as an example, these criteria can be used to rate studies in any indication.

Clinical studies

1. *Is the study randomised and double-blind?*

High-quality Grade A studies must be randomised and double-blind in design, to avoid the risk of biasing the results. The design may be parallel-group or crossover, although the former is mostly used in migraine studies. Drugs that appear to be effective in open studies and case series frequently fail to perform as well when the patients and physicians are blinded to the treatment given.

2. *Is the study placebo-controlled?*

The placebo effect can be very powerful, particularly in migraine studies, where the placebo response is high and variable (see Figure 1). An objective response to a drug can only be observed when placebo is used as the comparator. The US FDA insists on a positive response from two placebo-controlled studies before they license a drug. Even when comparing two active drugs, it is useful to include a placebo arm to unequivocally demonstrate the effectiveness of the therapies.

3. *Is the patient group appropriate to the study being conducted?*

The patients selected for all studies should be representative of typical sufferers of the illness in terms of age range, gender and race. This is vitally important for migraine studies, where sufferers are mostly female and young to middle-aged adults.

4. *Is the diagnosis confirmed?*

Definitive diagnostic criteria are required for the inclusion of patients in all studies. Migraine may easily be confused with tension-type headache or chronic daily headache if rigorous criteria are not used. The gold standard is to use the International Headache Society classification, which has recently been updated.[4]

5. *Is the study powered appropriately?*

In the statistical methodology section of the article, there should be text explaining the 'power' of the study. This refers to the numbers of patients necessary in each group for the study to have sufficient statistical power to distinguish between the treatments with the endpoints used. For migraine studies, over 100 patients in both active treatment and placebo groups are generally required, and several hundred to a thousand or more in studies of two active treatments.

6. *Are the study endpoints valid and clinically relevant?*

Clinical study endpoints should be statistically valid and clinically meaningful. The gold standard endpoint in migraine studies is headache improvement, with an improvement from severe or moderate to mild or none ('headache relief') or improvement from any grade to pain-free status ('complete headache relief') the most frequently used. Such categorical scales are easy to understand and interpret. Continuous visual analogue scales should be avoided due to difficulties in interpretation. Alternative endpoints include patient preference, the level of impact, quality of life and treatment need, but these should be used as secondary endpoints, at least for now.

7. *Is safety and tolerability being assessed?*

All studies should include measurements of the tolerability of the drug, assessed as the incidence and severity of adverse events. These include any event after taking the drug, irrespective of causality. In this way they differ from side effects, which occur as a direct result of the drug. Many Grade B studies have tolerability as their primary endpoint, particularly in long-term open-label studies. Safety is also sometimes assessed, usually in terms of blood pressure, heart rate and liver function.

Evidence from other sources

Meta-analyses

Meta-analyses are used to combine data from several studies to obtain more robust data than are available from the original studies. Systematic meta-analyses combine individual patient data from all studies conducted with a drug, both published and unpublished. Such analyses are considered Grade A evidence and can be used in treatment recommendations. Several meta-analyses have been conducted with the triptans, but only one meets the above criteria, although even this has been criticised in terms of its methodology, statistical analyses and the clinical significance of its results.[5] This meta-analysis showed that all oral triptans are effective migraine treatments, and that differences between them are relatively small. Non-systematic meta-analyses use selected clinical data and often artificially-produced endpoints. They provide Grade B clinical evidence at best.

Post hoc analyses of study data

Post hoc analyses (sometimes known as 'data mining') are additional analyses conducted on a study that were not specified in the protocol. They are frequently conducted by pharmaceutical companies attempting to differentiate their drug from those of their competitors.

Analyses frequently conducted with the triptans include:

- 'Therapeutic gain' (TG: response of active drug minus response from placebo).
- 'Number needed to treat' (NNT: the number of patients that need to be treated to achieve a successful response, corrected for placebo, i.e. the reciprocal of therapeutic gain).
- Ad hoc endpoints, e.g. improvement in nausea, patient satisfaction, sustained pain-free responses and some economic analyses.
- Descriptive reviews of selected studies.

None of these analyses provides more than Grade B evidence. There is a good argument that analyses of TG and NNT should not be conducted, due to the variable placebo response rate in migraine studies.

In conclusion, large, randomised, double-blind, placebo-controlled clinical trials form the gold standard of clinical evidence for evaluating medications (Grade A). Non-randomised studies and meta-analyses and *post hoc* analyses can only provide supporting data (Grade B/C).

Continued from page 1

Several conclusions can be made from these data:

1. All the triptan drugs evaluated in these studies are significantly superior to placebo in terms of headache relief, and therefore possess Grade A evidence of efficacy.
2. The placebo response rate is highly variable, ranging from < 20% to > 40%.
3. Most of the oral triptan formulations provide broadly similar levels of headache relief, although efficacy may vary in different studies of the same drug. However, naratriptan and frovatriptan may have lower reported 2-hour efficacy rates compared with the other oral triptans.

The way forward: developing new study endpoints for migraine studies

While it is difficult to distinguish between the triptans in clinical studies, preference studies clearly demonstrate that patients can distinguish between triptans and non-triptans, and even between different triptans. This incongruity may be due to the relative insensitivity of the standard clinical trial endpoint, relief of headache. New and more sensitive clinical trial endpoints are required for use in clinical studies that reflect everyday general practice (naturalistic studies). Among the potential endpoints that have been used are assessments of:

- Patient preference
- Impact on the patient's daily life
- Quality of life.

However, novel endpoints for migraine studies are still required that are simple to use and summarise the whole migraine experience. Recently, a new questionnaire, the Migraine Assessment of Current Therapy (Migraine-ACT) has been developed as a screening tool to identify patients who require a change in their acute medication. This questionnaire (Table 2) is brief and simple to use, as well as being a reliable and valid measure of migraine severity.[3] We hope that questionnaires such as Migraine-ACT will be used in clinical studies and prove to be sensitive outcome measures.

Please answer all four questions below, as 'yes' or 'no', by placing a tick in the relevant box.

Question	Yes	No
When you take your treatment: **Does your migraine medication work consistently, in the majority of your attacks?**		
When you take your treatment: **Does the headache pain disappear within 2 hours?**		
When you take your treatment: **Are you able to function normally within 2 hours?**		
When you take your treatment: **Are you comfortable enough with your medication to be able to plan your daily activities?**		
Migraine-ACT Score		

Table 2. The 4-item Migraine-ACT questionnaire recommended for use in primary care.

Scoring the Migraine-ACT questionnaire

One or more 'no' answers may indicate the need to change treatment. An increasing number of 'no' answers indicates increasing treatment needs.

References

1. Dowson AJ et al. Headache Care 2005;2: in press.
2. Silberstein SD, for the US Headache Consortium. Neurology 2000;55:754–62.
3. Dowson AJ et al. Curr Med Res Opin 2004;20:1125–35.
4. International Headache Society. Cephalalgia 2004;24 (Suppl 1):1–160.
5. Ferrari MD et al. Lancet 2001;358:1668–75.

Acknowledgements

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