

## **Guidelines for Controlled Trials of Drugs in Migraine. First Edition**

International Headache Society Committee on Clinical Trials in Migraine

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# Guidelines for controlled trials of drugs in migraine. First edition

## International Headache Society Committee on Clinical Trials in Migraine

### Cephalalgia

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The present guidelines were developed under the auspices of the International Headache Society because of a need "to improve the quality of controlled clinical trials in migraine". Quality controlled trials are the only way to demonstrate convincingly the efficacy of a drug. Only quality trials can form the basis for international collaboration on drug therapy.

A controlled clinical trial in migraine should be regarded as a scientific experiment in which a relevant question is answered. The trial can be either pragmatic, asking questions about the impact on health of a drug, or explanatory, testing the efficacy of a drug in migraine (1). The guidelines given are principally for explanatory trials, since the experience with clearly pragmatic trials in migraine is almost non-existent. Furthermore, the traditional classification drug trials into phase I-IV studies will generally be avoided in these guidelines, since migraine trials do not differ in this respect from trials in other conditions. Concerning these and other issues applying to clinical trials in general the reader should consult general works on clinical trial methodology (2-5). Here, only issues of specific relevance to migraine will be taken into account. Previous discussions on these issues have been reported (6-11).

Migraine can be treated with drugs for the acute attack or with prophylactic drugs. Naturally, trials concerning these two aspects of migraine therapy will have quite different designs, and the guidelines have separate sections to deal with these. Each section consists of the following subsections: patient selection, trial design, evaluation of results, and statistics. A short section on ethics is also included. At the end, checklists for drug trials concerning both acute and prophylactic treatments are given.

Based on the experience of the committee members and in some cases on analysis of previous trials, recommendations on the various points are given. Only a few are firm recommendations, and none should be regarded as dogmas. As is hopefully reflected in several of the comments to the recommendations, different solutions to the problems can be equally appropriate.

The main purpose of these guidelines is to draw the investigators attention to the problems inherent in drug trials in migraine.

#### 1. Ethical considerations

There are no ethical matters specific to migraine. Controlled trials in migraine should be performed, as for any drug trial, in accordance with the Declaration of Helsinki II.

The use of placebo in migraine trials is justifiable only in high-quality trials and if the scientific question cannot-be solved without the use of placebo (see sections 2.2 and 3.2 on trial design).

2. Drug trials dealing with treatment of the acute attack In trials dealing with the treatment of the migraine attack one should be aware that the pain is not a stable pain, but often a gradually developing pain which reaches a peak with subsequent spontaneous resolution. This poses problems regarding the timing of intake of test medication, either early or when the attack is fully developed, and in the evaluation of results.

In migraine with aura there is the option for treatment during the aura phase and thus studying protection against the headache phase. This option should be the subject of special trials.

### 2.1 Selection of patients

**2.1.1 Migraine definition.** Recommendations: The diagnostic criteria will conform to those of the IHS (Cephalalgia 1988:8 (suppl 7); 1-98).

Comments: Criteria of the IHS should be strictly adhered to. It is well recognized that there are patients who do not conform to the IHS criteria but, nevertheless, are diagnosed as having migraine, are treated accordingly and who respond appropriately. For clinical drug trials, however, requirements are more rigid than in clinical practice. Relatively few patients will be excluded by requiring IHS criteria.

The IHS diagnostic criteria classify attacks. Some patients have attacks both with and without aura in their Life time. Thus some patients can be classified as migraine patients with aura, without aura, and with and without aura. If patients are to enter a trial specifically concerning migraine with aura, one could arbitrarily rule that they should have had more than 90% of attacks with aura during the last 2 years, and similarly more than 90% of attacks for migraine without aura. During the trial each attack should be classified according to the IHS criteria and these data should be reported. Only attacks with or without aura should be studied in a particular trial.

Regarding the separation of migraine without aura and tension-type headache, consult the IHS criteria.

**2.1.2 Interval headaches.** Recommendations: Interval headaches are permitted if they are well recognized by the patient. The patient should be able to differentiate migraine from an interval headache by the quality of pain (one-sided, pulsating, moderate or severe intensity) and/or by associated symptoms (nausea, discomfort to light or sound, visual symptoms or other aura). Early safety and efficacy studies should not include interval headache.

Comments: Future studies may show that interval headaches are indeed fragments of migraine without aura but, for the present, one must exclude those patients who cannot distinguish interval headaches from typical migraine without aura.

**2.1.3 Frequency of attacks.** Recommendations: Attacks of migraine should occur one to six times per month. The frequency of interval headaches should be no more than 6 days per month. There should be at least 24 h of freedom from headache between attacks of migraine.

Comments: The numbers in this section are arbitrarily derived. In order to avoid very long trials a minimum of one attack per month is recommended. The maximum frequency of six per month is not absolute and allows for more rigid standards in certain trials. Interval headaches of more than six per month may blend into attacks of migraine without aura if migraine were also to occur as often as six per month. Twenty-four hours of freedom between attacks of migraine permits identification of individual attacks and avoids multiple treatments within one prolonged attack.

**2.1.4 Duration since onset.** Recommendations: Migraine attacks should have been present for more than one year.

Comments: Because there are no objective signs of migraine, a minimum course of one year is advisable to help exclude other types of headaches which may mimic migraine. At least five and two prior attacks of migraine are essential for the IHS criteria of migraine without and with aura, respectively.

**2.1.5 Duration of observation.** Recommendations: There should be a 3-month well documented retrospective history or one month prospective baseline recording.

Comments: Prospective observation is not essential in drug trials evaluating acute treatment for migraine.

**2.1.6 Age at onset.** Recommendations: The age at onset of migraine should be less than 50 years.

Comments: Migraine beginning after the age of 50 is atypical and headache onset in these years is often due to underlying organic disease that sometimes mimics migraine. Few patients will be excluded by this limitation.

**2.1.7 Age at entry.** Recommendations: Patients may be entered into the study between the ages of 18 and 65 years.

Comments: A special protocol will be required for children (under the age of 18)(12). Migraineurs over the age of 65 are subject to cerebrovascular disease and other illnesses that increase the hazard in using experimental drugs.

2.1.8 *Sex.* Recommendations: Both male and female patients are acceptable.

Comments: There are more women than men in the migraine population. In most migraine trials, however, this female preponderance is exaggerated. Efforts should be made, therefore, to recruit as many males as possible.

2.1.9 *Concomitant drug use.* Recommendations: Other concomitant therapy is undesirable. In early trials of safety and efficacy, the patient should not take any other drugs. In later trials contraceptive drugs and other drugs not taken for migraine are not contraindicated if there are no important side effects or interactions and the dose has been stable for 6 months.

Withdrawal of prophylactic drugs prior to entry should have occurred at least one month beforehand.

Excluded are the following: patients who abuse drugs for headache, that is, take medication for acute headache on more than 10 days per month; patients who abuse alcohol or other drugs (DSM-III criteria); patients who are allergic to compounds similar to the trial drug; patients who have taken antipsychotic or antidepressant medication during the 3 months prior to the study; sexually active women who do not practice contraception.

Comments: To exclude patients who occasionally use a sedative or minor tranquilizer or to exclude those women who experience no difficulty using contraceptive drugs would too severely limit the study population. On the other hand, it is desirable to eliminate patients who take excessive drugs for the treatment of acute headache or who abuse drugs or alcohol. Those people who are known to be resistant generally to antimigraine drugs may unfairly bias the study. However, unresponsiveness to medication may be due to inadequate dose, short duration of trial or other factors. These patients are not unequivocally excluded, but the investigators should set up criteria for their inclusion in the protocol.

## 2.2 *Trial design*

2.2.1 *Blinding.* Recommendations: Controlled trials concerning acute treatment should be double-blind.

Comments: Open or single-blind design may be feasible in certain pilot studies. Apart from these trials, drugs used for acute treatment of migraine can only be reliably evaluated in randomized, double-blind trials.

2.2.2 *Placebo control.* Recommendations: 1. Drugs used for the acute treatment of migraine should be compared with placebo. 2. When two presumably active drugs are compared, placebo control should also be included in order to test the reactivity of the patient sample. 3. When a new drug is presumably better than a standard drug and this is to be demonstrated in the trial, there is no need to include placebo.

Comments: The placebo effect in the treatment of migraine attacks varies from 15% to 70%, and a drug should therefore be demonstrated to be superior to placebo. That two presumably active drugs are not significantly different in the trial is no proof of efficacy or comparability. To refer to a previously found efficacy of the established drug is to use historical controls, a method largely discouraged in medicine. Both drugs should also be shown to be superior to placebo in the current trial. If a new drug is found superior to a standard drug, the standard drug "will take the place of placebo", which in this case is not needed.

2.2.3 *Crossover / non-crossover.* Recommendations: Both crossover and non-crossover designs can be used.

Comments: The crossover design is probably considerably more powerful than the non-crossover design although no formal calculations have been performed. There is probably no risk of a carryover effect in acute treatment, but a period effect using the crossover design has been observed in some trials.

If a drug is compared to placebo or an inferior drug, both designs can be used. However, if comparability of two drugs and at the same time superiority over placebo are to be demonstrated (cf. 2.2.2), then probably only the crossover design will result in narrow confidence intervals.

2.2.4 *Stratification.* Recommendations: There is no need for stratification in acute treatment trials.

Comments: Randomization alone does not ensure comparability among patients in the different treatment groups, and stratification for the most important prognostic factors should ideally be used. These prognostic factors are, however, virtually unknown in migraine.

2.2.5 *Dosage.* Recommendations: In assessing any new drug no assumptions should be made regarding dosage, and attempts should be made to test as wide a range as possible in different trials.

Comments: Ideally the doses should be derived from pilot studies establishing the therapeutic range of the drug in plasma. So far this therapeutic range has not been firmly established for any drug used in the acute treatment of migraine.

The choice of doses in comparative trials is difficult, since information about a dose-effect relationship in migraine treatment is lacking. There is presently no "scientific" solution to the problem. Instead good clinical judgements should be used.

**2.2.6 Route of administration.** Recommendations: In early trials to establish efficacy, parenteral therapy, if possible, is preferable.

Comments: Investigators should be aware of the often poor oral absorption during migraine attacks. Preferably, the drug should be investigated kinetically during migraine attacks in order to establish sufficient absorption before embarking on a controlled trial.

**2.2.7 Time of administration.** Recommendations: Timing of medication should address the problem of whether the drug should be given early or when the attack is fully developed.

Comments: Treatment should start preferably as early as possible to mimic clinical practice. However, in migraine without aura the patients may have difficulties in distinguishing between this and interval headache in the beginning of an attack, and may consequently treat interval headaches. Fully developed attacks are easily distinguished from interval headaches but some drugs, which are effective when taken early, may not be effective later in the attack. Preferably, a drug should be investigated both as early treatment and as a treatment for fully developed attacks.

**2.2.8 Number of attacks treated with same drug.** Recommendations: In a crossover trial, one or two attacks can be treated with the same drug. In a non-crossover trial, two to four attacks can be treated with the same drug.

Comments: Repeated intake of the test drug may be expected to increase the discriminative power of a trial. However, repeated intake of test medication prolongs the trial considerably, especially in cross-over trials, and patients often fail to treat all attacks if they are expected to treat more than four to six attacks (13,14,15). The increase in power by repeated intake is therefore often counterbalanced to some extent by the decrease in the number of patients treating all attacks. Furthermore, repeated intake of placebo should be limited.

Repeated administration on consecutive days of one and the same attack should not be accepted.

**2.2.9 Escape medication.** Recommendations: Escape medication should be allowed after <2 h.

Comments: In some cases with parenteral drug administration, escape medication could be used after, e.g. 60 min, but in most cases with oral administration it is preferable to wait 2 h before escape medication is allowed. Treatment is judged as a failure as soon as escape medication is taken (see comments under sections 2.3.2 and 2.3.5).

## 2.3 Evaluation of results

**2.3.1 Attack report form.** Recommendations: A simple report form suitable to answer the main objectives of the trial should be used.

Comments: Complicated report forms with detailed descriptions of symptoms of the actual attack may be difficult for patients to fill out during migraine attacks when at the same time they shall rate efficacy parameters.

**2.3.2 Number of attacks resolved within 2 h.** Recommendations: Number of migraine attacks resolved within 2 h, before any escape medication, should usually be the primary parameter of efficacy. Whenever an attack remits within 2 h, and relapses within 24 h, it is a treatment failure by this criterion (see comments).

Comments: This parameter is clinically relevant, simple and not affected by escape medication. It can be used in migraine attacks with aura as well as without aura. Resolution, not alleviation, within 2 h might seem unrealistic with some drugs. It is, however, difficult to choose a longer time than 2 h because, for practical and ethical reasons, patients should be allowed to take escape medication after no more than 2 h. This parameter is suggested as the primary but not the only one for efficacy.

With parental administration a drug may be quickly effective and the time point for resolution of the attack can be less than 2 h.

If a drug is effective quickly in bringing resolution of the attack, but the attack relapses because of a short duration of action of the drug (as has been observed in patients with longstanding attacks), repeated intake of the same drug can be optional; this requires a special study design.

**2.3.3 Duration of attacks.** Recommendations: Patients should note time of onset of attack, time of taking the test drug and time when the headache disappears. This allows calculation in hours of the total duration of the attack and the time between test drug intake and end of the attack.

Rules for temporary disappearance of headache: when an attack relapses within 24 h, even if the treatment seemed initially effective, it should be considered the same attack.

Comments: The duration of an attack is a complicated parameter. It is influenced not only by the test drug but also in a rather complicated way by the use of escape medication.

The rules given for temporary disappearance of headache are arbitrary, but appear the "least bad", and some rules are necessary to standardize evaluation of attack duration.

Only if the test drug is very successful in quickly aborting a migraine attack will the duration of that attack be an expression for efficacy; this situation is covered by section 2.3.2. In all other cases many factors influence duration of the attack. For this

reason duration cannot be recommended as one of the primary efficacy parameters.

**2.3.4 Severity of headache.** Recommendations: 1. The severity of a headache should be noted by the patient just before drug intake and 2 h later, before any escape medication, on a verbal scale: 0 = no headache; 1 = mild headache, allowing normal activity; 2 = moderate headache, disturbing but not prohibiting normal activity; bed rest is not necessary; 3 = severe headache, normal activity has to be discontinued. Bed rest may be necessary.

2. Alternatively, visual analogue scales may be used.

Comments: The recommended verbal scale takes into account not only the intensity of the headache but also the functional consequences of the attack on the patient's activity level, which is probably a good reflection of the severity of the headache. Similarly, the extremes of the visual analogue scales can be defined so as to take into account the total impact of the migraine attack on daily activities.

**2.3.5 Escape medication.** Recommendations: The use of escape medication 2 h (or before) after the intake of the test drug can be used as an efficacy parameter.

Comments: This parameter seems to correlate well with the patient's judgement of the efficacy of the test drug. It is, however, less sensitive than the main parameter, resolution of the attack within 2 h.

**2.3.6 Global rating of attack severity.** Recommendations: After the attack the patient can rate the attack on a verbal scale: mild, moderate, severe, excruciating.

Comments: When using this scale the patient should be asked to take into consideration severity and duration of pain, nausea and any other symptoms.

**2.3.7 Global evaluation of medication.** Recommendations: A simple verbal scale should be used by the patient: nil, moderate, good, excellent.

Comments: This criterion may be one of the most clinically relevant, taking into account both efficacy and tolerance; the latter excludes its use as the primary measure. It is probably best used in later trials.

**2.3.8 Presence of nausea and/or vomiting.** Recommendations: The presence of nausea and/or vomiting should be recorded at the time of intake of test medication and after 2 h.

Comments: Nausea/vomiting is too difficult to rate on a verbal scale. They can occur as a side effect of test medication and should therefore be noted for up to 2 h. After 2 h the occurrence of nausea/ vomiting may be due to escape medication.

## 2.4 Statistics

The recommended primary parameter of proportion of attacks resolved within 2 h per patient (and per treatment if crossover) can be used in calculations of sample size with standard statistical methods. The investigator thus needs to estimate the placebo response and define the difference to be detected.

Standard statistical methods can also be used for analysis of assessment parameters in both crossover and non-crossover trials.

A period effect has been found in some crossover trials and should be dealt with appropriately.

Confidence intervals for differences (16) are recommended in order to inform the reader fully of the results of the trial. A statement that two drugs are comparable without giving confidence intervals is unacceptable.

## 3. Drug trials dealing with migraine prophylaxis

In general, the subjective nature of migraine and a high placebo effect invalidate open and single-blind trials. However, regarding pilot studies performed in the early development of a new prophylactic drug for migraine one should distinguish between two situations: an established drug with a new indication of migraine prophylaxis; and a completely new drug which is being developed for migraine prophylaxis as its first indication. We recommend that with an established drug one should start directly with a double-blind pilot study, whereas with a new drug, open or single-blind pilot studies should be conducted. With a new drug kinetic studies should also be performed in the pilot studies (cf. acute).

When a possible prophylactic effect in migraine has been suggested by pilot studies, further double-blind, randomized, controlled trials should be performed. In these trials the drug should be compared with placebo and its efficacy relative to established drugs should preferably also be evaluated. Whereas there are generally no problems with the comparison with placebo (the drug should be demonstrated to be better than placebo in several studies), the comparison with established drugs often poses problems. Sometimes the new drug is found to be better than an established drug, but in most trials the two drugs are not found to be statistically significantly different. If the results of these trials are reviewed critically (17, 18), it is often apparent that the trials are too small to demonstrate comparability. Furthermore, if both drugs are found to be effective by comparison with a baseline period, the improve-

ments noted may be due to the natural history of migraine with amelioration purely with time (6). Therefore, comparative trials should also be placebo-controlled. The numbers of patients needed (see section on statistics) will therefore be, even in a cross over trial, so big that multicentre trials should be considered. If enough patients cannot be recruited for the trial it is better to avoid doing comparative trials with a low power.

As mentioned in the section on evaluation of results in the planning phase, only a few parameters should be defined as the primary evaluation parameters. However, in the first phase of the controlled evaluation of a drug, trials may be performed with the aim of evaluating efficacy on all possible parameters, a so-called "fishing experiment". Such trials should be regarded as hypothesis-generating and the results should subsequently be confirmed in regular hypothesis-proving trials.

### 3.1 Selection of patients

**3.1.1 Migraine definition.** Recommendations: The diagnostic criteria will conform to those of the IHS (Cephalalgia 1988:8 (suppl 7); 1-98).

Comments: Criteria of the IHS should be adhered to strictly. It is well recognized that there are patients who do not conform to the IHS criteria but, nevertheless, are diagnosed as having migraine, are treated accordingly and who respond appropriately. For clinical drug trials, requirements are more rigid than in clinical practice. Relatively few patients will be excluded by requiring IHS criteria. The IHS diagnostic criteria classify attacks. Some patients have attacks both with and without aura in their life time. Thus some patients can be classified as migraine patients with aura, without aura, and with and without aura. If patients are to enter a trial specifically concerning migraine with aura, one could arbitrarily rule that they should have had more than 90% of attacks with aura during the last 2 years, and similarly more than 90% of attacks for migraine without aura. During the trial each attack should be classified according to the IHS criteria and these data should be reported.

Regarding the separation of migraine without aura and tension-type headache, consult the IHS criteria.

**3.1.2 Interval headaches.** Recommendations: Interval headaches are permitted if they are well recognized by the patient. The patient should be able to differentiate migraine from an interval headache by the quality of pain (one-sided, pulsating, moderate or severe intensity) and/or by associated symptoms (nausea, discomfort to light or sound, visual symptoms or other aura). Early safety and efficacy studies should not include interval headaches.

Comments: Future studies may show that interval headaches are indeed fragments of migraine without aura but, for the present, one must exclude those patients who cannot distinguish interval headaches from typical migraine without aura.

**3.1.3 Frequency of attacks.** Recommendations: Attacks of migraine should occur two to six times per month. The frequency of interval headaches should be no more than 6 days per month. There should be at least 24 h of freedom from headache between attacks.

Comments: The numbers in this section are arbitrarily derived. The frequency of two to six per month allows for more rigid standards in certain trials. Interval headaches of more than six per month would begin to blend into attacks of migraine without aura if migraine were to occur as often as six per month. Twenty-four hours freedom between attacks of migraine permits identification of individual attacks.

**3.1.4 Duration since onset.** Recommendations: Migraine should have been present for more than one year.

Comments: Because there are no objective signs of migraine, a minimum course of one year is advisable to help exclude headaches due to organic disease that may mimic migraine, and to establish a stereotyped pattern for the patient's headaches.

**3.1.5 Duration of observation.** Recommendations: There should be a 3-month well documented retrospective history and a prospective baseline of at least one month.

Comments: The character, and especially frequency, of headaches as related retrospectively by the patient is often different from careful prospective observation by the physician and patient. Moreover, patients entering a study often show a change in the frequency of their attacks. Prospective observation will best define the frequency and prevent a reported, but unreal, change in frequency from being attributed to the study drug.

**3.1.6 Age at onset.** Recommendations: The age at onset of migraine should be less than 50 years.

Comments: Migraine beginning after the age of 50 is atypical and headache onset in these years is often due to underlying organic disease that sometimes mimics migraine. Few patients will be excluded by this limitation.

**3.1.7 Age at entry.** Recommendations: Patients may be entered into the study between the ages of 18 and 65 years.

Comments: A special protocol will be required for children (under the age of 18) (12). Migraineurs over

the age of 60 are subject to cerebrovascular disease and other illnesses that increase the hazard in using experimental drugs.

**3.1.8 Sex.** Recommendations: Both male and female patients are acceptable.

Comments: There are more women than men in the migraine population. In most migraine trials, however, this female preponderance is exaggerated. Efforts should be made, therefore, to recruit as many males as possible.

**3.1.9 Concomitant drug use.** Recommendations: Other concomitant therapy is undesirable. In early trials of safety and efficacy, the patient should not take any other drugs. In later trials contraceptive drugs and other drugs not taken for migraine are not contraindicated if there are no important side effects and the dose has been stable for 6 months.

Migraine prophylactic medication should be discontinued 3 months prior to the drug trial.

Excluded are the following: patients who abuse drugs for headache, that is, take medication for acute headache more than 10 days per month; patients who abuse alcohol or other drugs (DSM-III criteria); patients who are allergic to compounds similar to the trial drug; patients who have taken antipsychotic or antidepressant drugs during the past 3 months; sexually active women who do not practice contraception.

Comments: In evaluating a prophylactic drug, other prophylactic drugs must be eliminated. To exclude patients who occasionally use a sedative or minor tranquilizer or to exclude those women who experience no difficulty using contraceptive drugs would too severely limit the population. On the other hand, it is desirable to eliminate patients who take excessive drugs for the treatment of acute headache or who abuse drugs or alcohol. Those people who are known to be generally resistant to anti-migraine drugs may unfairly bias the study. However, unresponsiveness to medication may be due to inadequate dose, short duration of trial, and other factors. These patients are not unequivocally excluded, but criteria for their inclusion should be defined.

## 3.2 Trial design

**3.2.1 Blinding.** Recommendations: Controlled trials in migraine prophylaxis should be double-blind.

Comments: Open or single-blind pilot studies may be feasible in certain pilot studies (see introduction to this section). Apart from these trials, drugs for migraine prophylaxis can only be evaluated with double-blind techniques.

**3.2.2 Placebo-control.** Recommendations: 1. Drugs used for migraine prophylaxis should be compared with placebo. 2. When two presumably active drugs are compared, placebo control should also be included in order to test the reactivity of the patient sample. 3. When a new drug is presumably better than a standard drug and this is to be demonstrated in the trial, there is no need to include placebo.

Comments: The placebo effect in migraine prophylaxis is usually in the range of 20-40% and in some trials even higher, and a drug should therefore be demonstrated to be superior to placebo. That two presumably active drugs are found equally effective in a trial is no proof of efficacy or comparability. To refer to the previous efficacy of the established drug in other trials is not enough; this is using historical controls, a method largely discouraged in medicine. Both drugs should also be shown to be superior to placebo. (For further discussion on this point, see the introduction to this section.)

If a new drug is found superior to a standard drug, the standard drug "will take the place of placebo", which in this case is not needed.

**3.2.3 Crossover/non-crossover.** Recommendations: Both crossover and non-crossover designs can be used in certain situations.

Comments: There was no consensus in the committee on this issue. The advantage of the crossover design is that it is approximately eight times more powerful than the non-crossover design in prophylactic migraine trials (19). For certain non-crossover designs, however, the number of patients required is no more than two to four times the number required in a crossover design (20) (for further discussion see (11)). The drawbacks of the crossover design is the possibility of a carryover effect; the need for a long total period of treatment (extended by washout periods) that may cause problems with dropouts; and side effects can more easily affect blinding with this design. A period effect is not a problem with the crossover design, because suitable statistical techniques can deal with this (6).

When a drug is compared with placebo or an inferior drug both designs can be used if a carryover effect is not present. If there are indications from previous trials of a carryover effect, the non-cross-over design should be used.

In the comparison of two drugs and placebo, the three-way crossover design should be used. This design, if properly performed, is not invalidated by a possible carryover effect (19) and will result in narrow confidence intervals.

**3.2.4 Randomization.** Recommendations: 1. Patients should be randomized both in crossover and non-crossover trials in relatively small blocks. 2. For



the triple crossover design (two active drugs versus placebo) the Latin square method should be used.

Comments: Patients are often recruited to prophylactic migraine trials over extended periods. It is therefore preferable to randomize in relatively small blocks, because patient selection may vary with time. Randomization should occur after baseline.

**3.2.5 Stratification.** Recommendations: Patients should be stratified for numbers of migraine attacks (e.g. <3 attacks per 4 weeks or >3 attacks per 4 weeks) occurring during baseline. Stratification is not necessary in crossover trials.

Comments: Randomization alone does not ensure comparability among groups before treatment, and stratification for important prognostic factors should ideally be used. These prognostic factors are, however, virtually unknown in migraine. In some studies (e.g. 21) the extent of the prophylactic effect of drugs has varied depending on whether frequent or less frequent attacks were present. It is therefore reasonable to use frequency of attacks for stratification.

**3.2.6 Baseline recording.** Recommendations: A one-month baseline should be used.

Comments: During baseline, placebo can be given to exclude placebo responders. This will, however, in some cases hinder actual observation of the placebo response later in the trial; the use of placebo during baseline is optional.

**3.2.7 Duration of treatment periods.** Recommendations: Treatment periods of at least 3 months should be used.

Comments: Relatively long treatment periods are important for the power of the trial and also because the efficacy of many drugs develops gradually (i.e. needs some weeks before becoming fully established). Furthermore, only effects of sufficient duration are clinically relevant. With some drugs with long equilibration half-lives (21) longer treatment periods of 4-5 months may be necessary to demonstrate the potential efficacy.

**3.2.8 Washout periods.** Recommendations: In cross-over trials a washout period of one month should be used.

Comments: In the crossover design, the effect of treatment in one period must not affect the results in the subsequent period. Since drug effects are often slow in onset and wane gradually, a drug-free (placebo) washout period must be interposed between the trial periods. Its length must exceed the time taken to eliminate both the drug and its effect, which is often unknown. A washout period of one month is recommended as a practically feasible compromise.

**3.2.9 Dosage.** Recommendations: In assessing any new drug in migraine prophylaxis no assumptions should be made regarding dosage, and attempts should be made to test as wide a range as possible in different trials.

Comments: As long as the pharmacological background for the efficacy of certain drugs in migraine remains unknown, the choice of doses in trials is a purely empirical compromise between efficacy and side effects. The willingness of the patients to take the drug for months depends heavily on the ratio between efficacy and side effects. The choice of dose is therefore one of the crucial factors in determining the chances for a successful completion of the trial. This compromise tends to induce the use of suboptimal doses in prophylactic migraine trials.

Another, no less important problem, is the choice of doses in comparative trials. Since information about dose-effect relationships in migraine prophylaxis is lacking, there is "no scientific" solution to the problem. Instead good clinical judgements should be used.

Dose-ranging trials, i.e. dose titration on an individual basis, can be an alternative to testing a drug with different doses in different trials.

**3.2.10 Symptomatic treatment.** Recommendations: Patients should use their usual symptomatic treatment for acute attacks, but it should be ensured that this is kept constant for each patient during the trial.

Comments: In a few previous trials, symptomatic treatment of attacks has been regulated, but the symptomatic treatment will probably not be effective in all cases. Many patients have often, by trial and error, found symptomatic treatment to provide some degree of relief, and it is too much for patients to abstain from such treatment during prolonged periods.

In the few cases where patients are clearly using ineffective drugs or drug combinations for symptomatic treatment, the investigator should prescribe the most suitable acute treatment. (Concerning abuse of analgesics and ergotamine, see exclusion criteria under patient selection.)

**3.2.11 Control visits.** Recommendations: Patients should be seen every fourth week.

Comments: Relatively frequent control visits are important in order to check the headache diary and encourage the patient's continuation in the trial.

### 3.3 Evaluation of results

**3.3.1 Headache diary.** Recommendations: The evaluation of efficacy should be based on a headache diary, which should be consistent with what were identified as the assessment parameters, and should include no more.

Comments: The headache diary should be suitable for evaluating the assessment parameters chosen among those given below. Secondary interpretation by investigators, i.e. investigators' evaluation of efficacy, is not recommended. The details of diary design are a local issue.

**3.3.2 Frequency of attacks.** Recommendations: Frequency of attacks per 4 weeks should be the main efficacy parameter. The number of migraine attacks should be recorded irrespective of their duration, and the following rules should be used for separating an attack of long duration from two attacks: a migraine attack which ends or is interrupted by sleep and then relapses within 24 h should be recorded as one attack, and not two.

Comments: The above rules for distinction between one and two attacks are arbitrary (see comments under 2.3.3).

Some trials permit the inclusion of patients with interval headaches, but only if they are able to differentiate them from migraine attacks. The headache diary should differentiate between the two types of headache by simply asking the patient, "is this a true migraine attack or another headache?" When identified, interval headaches may simply be recorded by the number of days per 4 weeks with interval headache.

**3.3.3 Number of days with migraine.** Recommendations: Number of days with migraine per 4 weeks can be used as an assessment parameter.

Comments: Because of the difficulties mentioned under section 3.3.2 concerning defining the duration of a migraine attack the use of migraine days has been proposed as a simpler alternative (7). This parameter, which allows the use of a more simple headache diary, where the patient can indicate whether or not a migraine headache was present for each day, will probably be most useful in large-scale long-term pragmatic trials. In the same diary the patient can also indicate interval headaches, which possibly are migraine fragments.

In the earlier phases of drug evaluation, frequency of attacks should be preferred as the primary assessment parameter, since number of days with migraine mixes up the frequency and duration of attacks, the latter parameter being also dependent on acute treatment of attacks.

**3.3.4 Severity of attacks.** Recommendations: 1. The same verbal scale as given under section 2.3.4 should be used: 1 = mild headache, allowing normal activity; 2 = moderate headache, disturbing but not prohibiting normal activity; bed rest is not necessary; 3 = severe headache, normal activity has to be discontinued. Bed rest may be necessary.

2. Alternatively a visual analogue scale may be used.

Comments: For general comments see section 2.3.4. Furthermore, in prophylactic trials the patient is asked to rate, in a single value, the severity of an attack which sometimes is mild and perhaps later severe by "integrating severity over time". It is difficult to give simple or standardized rules for patients to use. One should be aware that patients are probably rating the maximum severity of the attack. Furthermore, acute treatment may possibly modify severity, independently of the trial drug.

Severity of headache should thus probably not be used as a primary efficacy parameter.

**3.3.5 Duration in hours.** Recommendations: Patients should be asked to record the time of the start of attacks and time of the end of attacks (in their view only), as raw data.

Comments: See comments under section 2.3.3. Furthermore, duration of attacks is modified by acute treatment, which cannot be standardized among patients. Measurement of duration is difficult because of uncertainties relating to time of onset, time of relief and interaction of sleep. Duration of attacks should therefore not be chosen as a primary efficacy parameter.

**3.3.6 Headache index.** Recommendations: The use of headache indices is not recommended.

Comments: Conceivably the headache indices (I = frequency X severity and II = frequency x severity x duration) reflect the total suffering of the patients. There are, however, considerable problems with both severity and duration (see comments under sections 3.3.3 and 3.3.4) and when used in the headache indices, faulty weighting in the arbitrary numerical severity score will be increased by multiplication. Most importantly, the headache indices can in no meaningful way be compared among subjects, and a certain decrease in a headache index is difficult to evaluate clinically. Lastly, there is no need for headache indices; in most cases where a decrease is found, this is due to a decrease in frequency of attacks (22).

**3.3.7 Drug consumption for symptomatic treatment.** Recommendations: 1. The number of migraine attacks per 4 weeks treated with symptomatic treatment should be given. 2. The number of tablets per 4 weeks, for example, should be recorded.

Comments: It is neither ethical nor practically feasible to standardize the symptomatic treatment used by the patients during a prophylactic drug trial. There is no satisfactory way of quantifying the consumption of symptomatic medication in relation to the different drugs used by the patients. Thus for the moment only the simple qualitative aspect of

## CHECKLISTS

### Acute attack treatment

2.1 Selection of patients criteria of IHS.		2.1.1 Migraine definition	Use diagnostic	
patient.	2.1.2 Interval headaches	Permitted if well recognized by the		
	2.1.3 Frequency of attacks	Migraine attacks: 1-6/month, interval headaches <6 days per month.		
	2.1.4 Duration since onset	>1 year.		
	2.1.5 Duration of observation	3 months retrospective or 1 month prospective recording.		
	2.1.6 Age at onset	<50 years.		
	2.1.7 Age at entry	18-65 years.		
	2.1.8 Sex	Both female and male patients.		
	2.1.9 Concomitant drug use	See text.		
	2.2 Trial design possible.	2.2.1 Blinding	Use double-blind technique.	
2.2.2 Placebo control		Use recommended, see text and ethical considerations.		
2.2.3 Crossover/non-crossover		Use both designs, see text.		
2.2.4 Stratification		Not recommended.		
2.2.5 Dosage		Use as wide a range of doses as		
2.2.6 Route of administration		In early trials use parenteral route, if possible.		
2.2.7 Time of administration		See text.		
2.2.8 Number of attacks treated		Crossover: 1 to 2 attacks,		
non-crossover: 2	with the same treatment	to 4 attacks.		
	2.2.9 Escape medication	Allowed after <2 h.		
2.3 Evaluation of results report form.		2.3.1 Attack report- form	Use a simple	
	efficacy,	2.3.2 Number of attacks	Should be primary parameter of	
		resolved within 2 h	see text.	
		2.3.3 Duration of attacks	Should be recorded, see text.	
		2.3.4 Severity of headache	Use a 4-point verbal scale or a visual analogue scale.	
		2.3.5 Escape medication	Can be used as an efficacy parameter.	
		2.3.6 Global rating of attack severity	Use a 4-point verbal scale.	
		2.3.7 Global evaluation of medication	Use a 4-point verbal scale.	
2.3.8 Presence of nausea and/or vomiting	Should be recorded.			
2.4 Statistics text.	Sample size calculations	Use primary efficacy parameter, see		
	Confidence intervals	Recommended.		

### Prophylactic treatment

3.1 Selection of patients criteria of IHS.		3.1.1 Migraine definition	Use diagnostic
patient.	3.1.2 Interval headaches	Permitted if well recognized by the	

whether or not a symptomatic treatment was taken during an attack can be used. This parameter can only be a secondary assessment parameter.

In within-patient comparisons the drug consumption can be used as a secondary assessment parameter, whereas its use is dubious in between-patient comparisons.

3.3.8 *Patient preferences*. Recommendations: The use of patient preferences is not recommended.

Comments: Patient preferences for one or other treatments can be asked only in a crossover trial. It is not recommended because it can endanger the blinding of patients since the design of the study has to be disclosed.

3.3.9 *Responders (50% effect)*. Recommendations: The number of responders can be expressed as those with a more than 50% reduction in attack frequency during treatment compared with the baseline period.

Comments: The choice of more than 50% reduction is traditional and arbitrary, and the investigator should be the judge of what he considers a good response. This parameter is insensitive, but can probably be used as a way of identifying, retrospectively, subgroups of responders. Such a retrospective analysis should then be confirmed in prospective trials with this problem as the main objective. Use of this parameter can thus only be considered as a hypothesis-generating exercise in most trials. Generalization of results of this sort (proportion of responders) is particularly difficult in view of the pre-selected nature of the study populations in a trial.

Alternatively, time series analysis (8, 23) can be used in defining responders.

### 3.4 Statistics

Calculations of sample sizes in prophylactic crossover and non-crossover trials, based on frequency of

CHECKLISTS (cont)

	3.1.3 Frequency of attacks	Migraine attacks: 2-6/month, interval headaches <6 days per month.
	3.1.4 Duration since onset	>1 year.
	3.1.5 Duration of observation	3 months retrospective and 1
prospective		recording.
	3.1.6 Age at onset	<50 years.
	3.1.7 Age at entry	18-65 years.
	3.1.8 Sex	Both female and male patients.
	3.1.9 Concomitant drug use	See text.
3.2 Trial design	3.2.1 Blinding	Use double-blind technique.
	3.2.2 Placebo control	Use recommended, see text and ethical consideration.
	3.2.3 Crossover/non-crossover	Use both designs, see text.
	3.2.4 Randomization	Randomize in small blocks.
	3.2.5 Stratification	Stratify for numbers of attacks during baseline.
	3.2.6 Baseline recording	A 1-month prospective baseline should
be		used.
	3.2.7 Duration of treatment periods	At least 3 months.
	3.2.8 Washout periods	1 month in crossover trials.
	3.2.9 Dosage	Use as wide a range of doses as
possible.		
the	3.2.10 Symptomatic treatment	Keep usual treatment constant during
		trial.
	3.2.11 Control visits	Every fourth week.
3.3 Evaluation of results	3.3.1 Headache diary	Use is recommended.
	3.3.2 Frequency of attacks	Number of attacks per 4 weeks should
be		the main efficacy parameter, see text.
parameter,	3.3.3 Number of days with migraine	Can be used as an assessment
		see text.
	3.3.4 Severity of attacks	Use a 4-point verbal scale or a visual analogue scale.
	3.3.5 Duration in hours	Should be recorded, see text.
	3.3.6 Headache index	Use is not recommended, see text.
	3.3.7 Drug consumption for symptomatic	Should be recorded, see text. treatment
	3.3.8 Patient preferences	Use is not recommended.
text.	3.3.9 Responders (50% effect)	Can be hypothesis-generating, see
3.4 Statistics	Sample size calculations	Use frequency of attacks, see text.
	Model	Separate therapeutic and "time effect"
in		crossover trials, see text.
	Confidence intervals	Are recommended.

attacks, have been published (24). Repeated analysis (19) of the relative power of the crossover versus the non-crossover design has confirmed that the former has eight times more power than the latter for detecting a certain effect. For practical purposes one can detect a difference with both designs. If, however, comparability between two drugs is to be demonstrated, only the crossover design will be suitable. In this case, as mentioned above, placebo should also be included, and this three-way crossover design, if properly conducted, is not invalidated by a possible carryover effect (19).

In the non-crossover design, comparisons between groups can be made either as comparisons during the treatment periods or as comparisons of changes from baseline. The latter is conceivably more powerful, but analyses have so far only shown a marginal increase in power (19). In non-crossover trials the use of the baseline value as a covariate should also be examined.

Suitable statistical methods (6) can be used in the crossover design for correction for a period effect ("time effect"), if present.

Confidence intervals for differences is recommended (16) in order to inform the reader fully of the results of the trial. A statement that two drugs are comparable without giving confidence intervals is unacceptable.

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*Note:* A revised second edition of these guidelines is planned in 3-4 years' time. Only practical experiences from presently ongoing trials, which also should be evaluated from methodological points of view, can lead to better guidelines. Investigators in the field are therefore hereby invited to criticize or comment on this first edition. Please write to:

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