Guidelines for trials of drug treatments in tension-type headache

First Edition: International Headache Society Committee on Clinical Trials in Tension-type Headache

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Introduction

a. General considerations

The present guidelines were developed under the auspices of the International Headache Society because of the need "to improve the quality of controlled trials of drug treatments in tension-type headache". They follow the *Guidelines for controlled trials of drugs in migraine* (1) and are presented along the same lines. Good quality controlled trials are the only way to demonstrate convincingly the efficacy of a drug, and form the basis for international agreement on drug therapy.

A controlled clinical trial in tension-type headache (TH) is a scientific experiment in which a relevant question is answered. The trial may be either pragmatic, questioning the impact on health of treatment, or explanatory, testing the efficacy of treatment in TH (2). These guidelines are principally for explanatory trials, since experience with clearly pragmatic trials in TH is almost non-existent.

The traditional classification of drug trials into phases I–IV is largely avoided in these guidelines, since TH trials do not differ in this respect from trials in other conditions. For these and other issues concerning clinical trials in general, the reader should consult works on clinical trial methodology (2–5). Only issues of specific relevance to TH are taken into account here.

b. Special clinical features

The presently used diagnostic criteria for episodic (ETH) (code 2.1) and chronic (CTH) (code 2.2) tension-type headache can be

found in the IHS Classification (1). Despite these apparently straightforward criteria, and that TH is the most frequent headache type in the general population (6), it remains the least characteristic of all headache types, its clinical diagnosis based chiefly on negative features (7). Some of the characteristics that may complicate patient selection and/or assessment of therapeutic effects include:

- TH has a *variable disease course*. The criterion by which the episodic and chronic forms is distinguished is headache frequency, the dividing line set arbitrarily at more than (chronic) or less than (episodic) 15 days per month or 180 days per year. The vast majority of people affected in the general population have a low frequency and do not consult a doctor (6). An estimated 3% have CTH and represent most of the TH patients consulting specialized headache/pain clinics (6).
- While migraine attacks are limited in terms of time, *attacks of TH may vary greatly in duration* from a few hours up to several days or weeks.
- *Diagnosis may be uncertain*, especially in TH of recent onset, or at the first consultation, because of the lack of specificity of diagnostic criteria or the presence of uncommon features. This probably explains why paraclinical investigations to exclude organic disease tend to be performed more frequently in TH than in headaches such as migraine. Episodic TH may be difficult to distinguish from migraine without aura. Electrophysiological as well as transcranial Doppler studies of groups of patients have shown that these two headache types may have pathophysiological features in common (8, 9). Modifications of the IHS diagnostic criteria have been proposed to distinguish better between migraine without aura and ETH (10, 11). As a further complication, both types of headache may coexist in a substantial number of people (12).
- *The intensity of pain in TH is generally less severe than in migraine* and there are usually no disabling accompanying symptoms. The degree of amelioration produced by effective therapy is thus less pronounced, suggesting that different, more sensitive, measures of efficacy might be useful in TH.
- *Poor compliance* may be a greater problem in TH patients than in migraineurs. Among several factors that could account for this (13) are less disability from TH, disappointment with treatment, and associated personality.
- The *exact pathophysiology* of TH *is unknown*. Some aspects may differ between the episodic and chronic forms (14). The IHS Classification subdivides TH into one subgroup "associated with disorder of pericranial muscles" (codes 2.1.1 and 2.2.1) and another without such a disorder (codes 2.1.2 and 2.2.2). There are at present no scientific data showing that these two subgroups differ pathophysiologically or in response to treatment.

● In the IHS Classification (1), the *fourth-digit code* is an attempt to indicate "*most likely causative factors*" in TH. These represent a wide variety of potential causes, but no clear evidence is yet available for some of the items. This subcategorization was proposed mainly for research purposes, but some items should be considered in drug trials as a means of obtaining homogeneous patient populations: overt oro-mandibular dysfunction (4th code 2), anxiety and/or depression (assessed according to DSM III-R criteria and on adequate scales/ inventories such as Bech's, Hamilton's or SCL-90R) should be excluded from TH trials and studied separately; similarly, patients with medication abuse/misuse should be excluded.
● *Non-drug therapies* are widely used in TH (15), and there is evidence from a limited number of controlled trials that some of them are effective. The guidelines presented here are for drug trials and need to be adapted for non-drug treatments, where additional problems, such as blinding and placebo control, have to be dealt with.

c. Drug trials in TH

Acute and prophylactic treatments have to be distinguished in TH, as in migraine. The TH attack can be used as a model for assessing efficacy and tolerability of analgesics (16–18). Single or repeated dosing can be used. Prophylactic trials are difficult to conduct in episodic TH because of the variability of the disease course. They are better in chronic TH, or in patients with frequent and regular attacks of episodic TH who may be close to the border between ETH and CTH.

Trials concerning these two aspects of TH therapy have quite different designs, and the guidelines have separate sections for these. Each section consists of the following subsections: patient selection, trial design, evaluation of results, and statistics. A short comment on ethics precedes the two major sections. Checklists for drug trials concerning both acute and prophylactic treatments are given at the end.

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 dogma. As reflected in several of the comments to the recommendations, other solutions to some problems can be equally appropriate.

The main purpose of these guidelines is to draw the investigator's attention to the problems inherent in therapeutic drug trials in TH.

d. Ethical considerations

Specific ethical problems related to TH are still to be defined. In the meantime, as in any therapeutic trial, controlled trials

should be performed in accordance with the latest version of the Declaration of Helsinki.

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

1. Trials dealing with the acute treatment of tension-type headache

Tension-type headache (TH) can be used as a pain model in assessing the efficacy and tolerability of analgesics in single or multiple dose clinical studies. Such studies should therefore conform in general to the FDA guidelines for the clinical evaluation of analgesic drugs (16).

1.1. Selection of patients

1.1.1. Diagnostic criteria

Recommendations: The diagnostic criteria should conform with those of the IHS (Cephalalgia 1988, Suppl 7) (codes 2.1 and 2.2). Either **ETH** or **CTH** patients should be selected.

Comments: Although the nosological borders of TH are still vague, the present IHS criteria are the best available and should be strictly adhered to. It is recognized that there are subjects whose symptoms do not conform to the IHS criteria but are nevertheless diagnosed as TH and, treated accordingly, respond appropriately. For clinical trials, however, requirements are stricter than in clinical practice. Relatively few subjects will be excluded if the required IHS criteria are not met. For acute drug trials, both the episodic (code 2.1) and the chronic (code 2.2) forms of TH can be studied, but including both types of patients in the same trial is not recommended.

If it is demonstrated in the future that the sub-groups "associated with disorder of pericranial muscles" (codes 2.1.1 and 2.2.1) and "not associated ?" (codes 2.1.2 and 2.2.2) have different pathogenetic mechanisms or respond differently to therapy, therapeutic trials should be directed towards one or the other subgroup.

Instruments, e.g. Headache Impact Questionnaires, may in the future allow the selection of patients on the basis of disease impact, in particular social and work impact (see 2.3.4.2) (19).

1.1.2. Associated migraine attacks

Recommendations: **Migraine attacks** are permitted if they are well recognized by the TH patient and if their frequency during the preceding year has **not exceeded one per month**. The patient should be able to differentiate migraine from TH by the localization, quality and intensity of the pain (unilateral, pulsating, moderate or severe intensity) and/or by associated symptoms

(nausea, sensitivity to light and sound, visual or other aura symptoms).

Early safety and efficacy studies should not include patients also experiencing migraine headaches.

Comments: Future studies may show that some attacks of TH are indeed fragments of migraine without aura but, for the present, patients who cannot distinguish migraine attacks from typical TH must be excluded. Exclusion of patients with migraine should not reduce the population by more than 10–15%.

1.1.3. Duration of headache

Recommendations: Although diagnostic criteria allow for shorter duration, it is recommended in clinical trials that only patients who usually have headache episodes of **no less than 4 h** should be selected in order to avoid uncertainty of distinction of treatment effect from spontaneous resolution.

1.1.4. Frequency of headache

Recommendations: In order to avoid long trials patients should have TH on **at least 2 days per month**.

Comments: The numbers of days in this section are derived arbitrarily. A minimum of 2 days of headache per month is recommended in trials on ETH, according to the IHS diagnostic criteria, an upper limit of 15 days of headache. CTH patients will by definition have between 15 and 31 days of headache per month, although many will have daily headache.

1.1.5. Duration since onset

Recommendations: TH should have been present **for at least 1 year**.

Comments: Because there are no objective signs of TH, a minimum course of 1 year is advisable to help exclude other types of headaches which may mimic TH.

1.1.6. Duration of observation

Recommendations: There should be a **3-month, well-documented retrospective history** of at least 6 headache days in ETH and at least 45 in CTH and/or **a 1-month prospective** baseline recording at least 2 headache days in ETH and at least 15 in CTH.

Comments: Prospective observation is *not essential* in drug trials evaluating *acute* treatment of TH.

1.1.7. Age at onset

Recommendations: In TH, age at onset should be **below 50 years**.

Comments: TH beginning after 50 years is often atypical and headache onset may be due to an underlying organic disease that mimics TH. Few patients will be excluded by this limitation.

1.1.8. Age at entry

Recommendations: Patients may be entered into the study at **between 18 and 65 years** of age.

Comments: A special protocol will be required for children (under the age of 18) (20). Patients over the age of 65 are subject to cerebrovascular disease and other illnesses that increase the hazard in using experimental drugs and the difficulties in assessing outcome.

1.1.9. Sex

Recommendations: Both **male and female** patients can be considered.

Comments: There are more women than men in the TH population (6). In many trials, however, this female preponderance is exaggerated. Efforts should therefore be made to recruit *as many males as possible*. Sexually active women who do not practise contraception should be excluded. Patients in whom there is a close association between the occurrence of TH and commencement of hormonal contraception should be excluded. TH appearing exclusively during the perimenstrual period can be studied in adequately designed trials.

1.1.10. Concomitant drug use

Recommendations: **No analgesic or psychotropic drug should be allowed in the 24 h prior to administration of the test drug**. In early trials of safety and efficacy, the patient should not be taking any other drugs. In later trials, contraceptive and other regularly taken drugs, not for TH, 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, taking analgesics or other drugs for acute TH on more than 10 days per month; patients who abuse alcohol or other drugs (DSM III-R criteria); patients who are allergic or hypersensitive to compounds similar to the trial drug; patients who have taken antipsychotic or antidepressant medications during the previous month.

Comments: Some long-acting non-steroidal anti-inflammatory drugs, notably oxicams (half-life 40–70 h), should not be allowed for longer periods before treatment. To exclude patients who occasionally use a sedative or minor tranquillizer, or to exclude women who experience no difficulty using contraceptive drugs, would too severely limit the population and would serve no obvious purpose. However, it is desirable to eliminate patients

who take excessive drugs for the treatment of acute headache, or who abuse drugs or alcohol, because of altered pathophysiology. Those patients who are known to be resistant to anti-headache drugs may unfairly bias the study. But, unresponsiveness to medication may be due to inadequate dose, short duration of use or other factors. These patients are not unequivocally excluded, but investigators should set up criteria for their inclusion in the protocol.

1.2. Trial design

In general, the guidelines for the Clinical Evaluation of Analgesic Drugs, phase II and III trials, defined by the FDA (17) should be followed.

1.2.1. Blinding

Recommendations: Controlled trials of acute treatment should be **double blind**.

Comments: Open or single-blind design may be feasible in exceptional circumstances. Outside these, acute treatments of TH can be reliably evaluated only in double-blind conditions that prevent biased assessment.

1.2.2. Randomization

Recommendations: Controlled trials of acute TH treatments should use random allocation to treatment groups.

Comments: Bias in allocation to treatments can be prevented only by randomization.

1.2.3. Placebo control

Recommendations: 1. Treatments of acute TH should be compared with **placebo**. 2. When two presumably active treatments are compared, **placebo control** should always 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 the purpose of the trials is to demonstrate this, there is no necessity to include placebo.

Comments: The placebo effect in the acute treatment of TH has not yet been adequately assessed. There is some evidence (13, 16, 18) that it may be comparable to that found with acute migraine therapy, i.e. around 30%. Any trial of treatment should therefore aim to demonstrate superiority to placebo.

When a standard drug substitutes for the placebo in a comparative trial, the conclusion is of limited value if no statistical difference is observed between the two drugs. That two presumably active treatments are not significantly different in a trial is

no proof of efficacy or comparability. To refer to the previously found efficacy of an established treatment is a use of historical controls, a method largely discouraged in medicine. Both treatments should also be shown to be superior to placebo in the current trial.

1.2.4. Crossover/parallel design

Recommendations: **Both** crossover and parallel designs may be used.

Comments: The crossover design is more powerful than the parallel design, although no formal calculations have been performed. There is unlikely to be any risk of a pharmacological *carry-over effect* in acute treatment so long as a sufficient time span (at least 48 h and/or at least four elimination half-lives of the test drug) separates successive dosings. A *period effect* has been observed in some crossover trials. If a drug is compared with 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 only the crossover design is likely to result in narrow confidence intervals.

1.2.5. Stratification

Recommendations: There is no need for stratification in acute treatment trials at the present time.

Comments: Randomization alone does not ensure comparability among patients in the different treatment groups, and stratification for the most important prognostic factors ideally should be used. These prognostic factors are virtually unknown in either of the two forms of TH, however. In future trials, stratification may become necessary according to TH subtypes (codes 2.1.1–2.2.1 vs. 2.1.2–2.2.2), 4th-digit codes, number of headache days, disease impact, etc. (see Introduction b & 1.1.1).

1.2.6. 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 or in different groups of patients in the same trial. The minimum effective dose should be defined in dose-finding studies.

Comments: Determining dose in trials comparing two active drugs is difficult, since information about dose–effect relationship in TH treatment is often lacking. There is presently no scientific solution to the problem. Instead, good clinical judgement should be used. There is no justification for the deliberate use of a subtherapeutic dose of a standard treatment: placebo should be used instead.

1.2.7. Route of administration

Recommendations: **Any** route of administration may be used, as appropriate to the drug.

Comments: Contrary to what is known of migraine attacks, there is at present no evidence suggesting that oral absorption is poor during TH. Nevertheless, a drug should be investigated kinetically during TH in order to establish sufficient absorption before embarking on a controlled trial.

1.2.8. Timing of administration

Recommendations: Patients should be instructed to take the drug when **headache intensity is at least moderate**.

Comments: This recommendation has proved to be satisfactory in several studies of acute TH drug treatment (13, 16, 18). Mild headaches, which are frequent in the general population, and very severe (or unbearable) TH, which is rare and may be confounded with migraine, need adequately adapted designs.

1.2.9. Number of headaches treated with the same treatment

Recommendations: In both crossover and parallel trials **one or two headaches** can be treated with the same drug. The **interval** between successive treatments should be **at least 48 h**.

Comments: It can be assumed that repeated use of the test drug for multiple treatments will increase the discriminative power of a trial. However, repeated use of test medication prolongs the trial considerably, especially in crossover trials, and patients often fail to treat all episodes if they are expected to treat more than two headaches (21, 22). The increase in power by repeated use may therefore be counterbalanced to some extent by the decrease in number of patients completing treatment of all attacks. Furthermore, repeated use of placebo should be limited on ethical grounds. Repeated administrations on consecutive days of a single headache episode should not be accepted.

1.2.10. Escape medication

Recommendations: Escape medication **must be allowed**.

Comments: In some cases with parenteral drug administration escape medication could be used after 60 min, but in most cases with oral administration it is preferable to wait 2 h before escape medication is allowed. Treatment is judged a failure if escape medication is taken before the period of evaluation is complete. See comments under 2.3.2 and 2.3.5.

1.2.11. Repeated dose studies and long-term trials

Recommendations: If a drug is known to be effective as an acute treatment of TH, it is recommended that its **tolerance** and **abuse**

potential be evaluated in long-term trials. Moreover, it may be worthwhile examining its **potential prophylactic effect** in trials designed as recommended in section 2.

1.3. Evaluation of results

1.3.1. Headache diary

Recommendations: A **simple diary** suitable for answering the main objectives of the trial should be used. The effect on the headache should be scored by the patient at **regular time intervals**, at least at 0 h, 2 h and 24 h. Shorter time intervals (e.g. 30 or 60 min) and shorter total scoring periods can be used if early effectiveness is expected.

Comments: Because of the discomfort of headache, measuring instruments should be as simple as possible. The time intervals at which effects are measured depend on the route of administration and the pharmacokinetic profile of the drug. Short intervals are necessary if the objectives require information on the speed of action of a drug. Twenty-four hours is proposed as a minimum total time span of scoring for headache recurrence and delayed adverse effects to be assessed.

1.3.2. Effect measures

1.3.2.1. Headache severity

Recommendations: Severity of the headache should be noted by the patient on a categoric, **verbal rating scale (VRS)** (0=no headache; 1=mild headache; 2=moderate headache; 3=severe headache) **and/or** on a **visual analogue scale (VAS)** (e.g. 100 mm with "none" and "very severe" at either end).

Comments: Experience with the VAS is limited in TH trials. However, as mentioned above, the pain in TH is usually mild or moderate. The categoric verbal scale, commonly used for migraine attacks, may therefore not be sensitive enough. The scales may also take into account the impact of the headache on daily activities; although this parameter is less important in TH than in migraine, where symptoms other than pain contribute to disability, it is still very relevant to patients. The terms "mild", "moderate" and "severe" for headache pain are often defined in functional terms: "can perform all activities", "cannot perform some activities", "cannot perform any activities".

1.3.2.2. Headache relief

Recommendations: It is recommended that the patient be asked to indicate not only the severity of the headache, but also the degree of relief of headache at a time period after therapy. This should be done on a **categoric scale** (0=no relief; 1=a little relief; 2=some relief; 3=much relief; 4=complete relief).

Comments: Scoring relief may be a more accurative way of assessing the effect of treatment in TH. The term "meaningful relief" is clinically relevant (23) and has been effectively used in migraine studies even though its definition is vague. In studies of analgesics, verbal pain relief scales have been slightly more sensitive than VAS or verbal pain scales (24). The design of the headache relief scale can allow for scoring increasing pain (e.g. −1=worsening) (13), which may be of importance when the trial medication is taken before the headache becomes maximal.

1.3.2.3. Global evaluation of treatment

Recommendations: **A simple verbal scale** should be used by the patient after each treatment: nil, moderate, good, excellent.

Comments: This criterion may be one of the most clinically relevant, taking into account as it does both efficacy and tolerance, the latter excluding its use as a primary efficacy measure. It is probably best used in later trials. Patients can also be asked to compare the trial drug(s) with the medication they usually use to treat their headache, responses being given for example on a 7–category "Comparative Evaluation" scale ranging from −3="much worse" to 0="same" to +3="much better".

1.3.3. Efficacy parameters

1.3.3.1. Number of headaches resolved at 2 h before any escape medication.

1.3.3.2. Headache intensity differences (HID scores), i.e. the arithmetic difference between the pretreatment headache intensity score and the score after each given time interval after dosing, for both the verbal rating scale (HID VRS) and the visual analogue scale (HID VAS).

1.3.3.3. Headache relief (HER scores), i.e. the VRS headache relief score at each given time interval after dosing.

1.3.3.4. Use of escape medication 2 h after administration of the trial drug.

1.3.3.5. Area under the time–response curve, calculated for change in headache intensity (SHID: sum of HIDs after every time interval) and headache relief (TOTHER: sum of HERs after every time interval).

1.3.3.6. Comparative global evaluation by the patient.

Comments: There are at present no scientific data that allow us to propose with confidence one of these parameters as the *primary efficacy parameter*. However, it can be extrapolated from trials in migraine and in other pain syndromes (17) that 1.3.3.1 (resolution

of headache at 2 h), 1.3.3.2 (HID scores) or 1.3.3.3 (HER scores) should be chosen as primary efficacy parameters. Number of headaches resolved at 2 h seems of most use in episodic tension-type headache, while HID and HER appear more adapted for the chronic form.

The acronyms HID and SHID, HER and TOTHER are adaptations to headache of PID (pain intensity differences) and SPID (sum of PIDs), of PAR (pain relief) and TOTPAR (sum of PARs) used in other pain syndromes (10).

After parenteral administration a drug may be effective more quickly, and the time point for resolution of the headache can be less than 2 h. If a drug acts rapidly, but the headache relapses because of a short duration of action (as has been observed in migraine), repeated intake of the same drug could be desirable; this, however, requires a special study design (see 1.2.11).

It has been argued that the above-mentioned parameters (HID, SHID, HER and TOTHER) are adequate for evaluating the difference in magnitude of effects among treatments over time, but that they give no reliable information on the probability of obtaining a clinically significant response (i.e. of achieving onset), the probability distribution of time to onset, the probability of cessation of the clinically significant response, and the probability distribution of the duration of effect. Hence an experimental paradigm that allows measurement of onset and duration of clinically significant (or meaningful, see 1.3.2.2) relief in time (the patient uses a stopwatch) has been proposed, as well as statistical models adapted to it (23).

1.4. Statistics

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

Standard statistical methods can also be used for analysing efficacy and tolerability 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 (25) are recommended, fully informing the reader of the meaning of the results of the trial. A statement that two treatments are comparable without giving confidence intervals is unacceptable.

2. Trials dealing with prophylaxis of tension-type headache

Although the following section covers prophylactic treatment of TH, i.e. prevention of the occurrence of headache, it has to be kept in mind that certain drugs may not have a prophylactic action in

the strict sense. For instance in chronic TH, because of the (almost) daily occurrence of headache and the frequent onset at awakening, drugs with analgesic properties may act as "daily acute therapies" producing global effects comparable to those of true prophylactics. There is at present no simple way of distinguishing between these two modes of action in a clinical trial. Whatever the mechanism, the clinical trial design will have the features of a long-term treatment with repeated administrations. Since "daily acute therapy" may lead to secondary headache, trials may need to be prolonged into a withdrawal period after the course of treatment.

In general, the subjective nature of TH and a *high placebo effect* (20 to 30%) (4) invalidate open and single blind trials, which can be accepted only in exceptional circumstances (see 1.2.1).

A new drug should be compared with placebo and preferably its efficacy with that of established drugs. Whereas there are generally no problems with the placebo comparison (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 the two drugs are found not to be statistically significantly different. If the results of such trials are reviewed critically in migraine (26, 27), it becomes apparent that the trials are often not sufficiently comprehensive to demonstrate comparability. Furthermore, if both drugs are found effective by comparison with a baseline period, the improvements noted may be due only to the natural history of TH with amelioration purely with time (regression to the mean) (8). Therefore, comparative trials should also be placebo controlled. The numbers of patients needed (see section on statistics) will therefore, even in a crossover trial, be so great that *multicenter trials* should be considered. It is better to avoid doing comparative trials with a low power if enough patients cannot be recruited, since these are only wasteful of resources and thus unethical.

As mentioned in the section on evaluation of results, only a few parameters (really only one) should be defined as primary efficacy parameters. However, in the first phase of the controlled evaluation of any treatment, trials may be performed with the aim of assessing efficacy on all possible parameters, a "*fishing experiment*". Such trials are merely "hypothesis-generating", the results subsequently being tested in regular "hypothesis-proving" trials.

2.1. Selection of patients

2.1.1. Diagnostic criteria

Recommendations: The diagnostic criteria should conform with those of the IHS (Cephalalgia 1988, Suppl 7) (codes 2.1 & 2.2). **ETH** or **CTH** patients can be selected.

Comments: (see 1.1.1.): Patients with overt depression (DSM-III-R criteria and pathological scores on scales for depression) should

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be excluded, as should those taking an analgesic on more than 15 days per month.

2.1.2. Associated migraine attacks (see 1.1.2)
2.1.3. Duration of headache (see 1.1.3)
2.1.4. Frequency of headache (see 1.1.4)

Comments: In order to avoid very long trials, the selection of patients with rare ETH is not recommended. Many patients with CTH will have (almost) daily headache. These patients seem more suited to prophylactic trials, but results from such studies cannot (necessarily) be extrapolated to ETH.

2.1.5. Duration since onset (see 1.1.5)
2.1.6. Duration of observation (see 1.1.6)
2.1.7. Age at onset (see 1.1.7)
2.1.8. Age at entry (see 1.1.8)
2.1.9. Sex (see 1.1.9)
2.1.10 Concomitant drug use (see 1.1.10)

Comments: When 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 and would serve no obvious purpose. 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, because of altered pathophysiology. Patients belonging within the diagnostic group "*Headache induced by chronic substance use or exposure*" (IHS Classification code 8.2) need to be studied in trials with a specific design. Patients who are known to be resistant to anti-headache drugs may unfairly bias the study. However, unresponsiveness to medication could be due to inadequate dosage, short duration of trial or other factors. These patients are not unequivocally excluded, but criteria for their inclusion should be defined.

2.2. Trial design

2.2.1. Blinding

Recommendations: Controlled trials of TH prophylaxis should be **double-blind**.

Comments: Open or single-blind controls may be feasible in certain pilot studies (see introduction to this section). Apart from these trials, drugs for TH prophylaxis can be reliably evaluated only in double-blind conditions if biased assessment is to be avoided.

2.2.2. Randomization

Recommendations: 1. Patients should be randomized in either crossover or non-crossover trials in relatively **small blocks**. 2. For

the triple crossover design (two active drugs vs placebo) the **latin square method** should be used.

Comments: Patients will be recruited to prophylactic TH 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, since many patients drop out or are excluded during this period.

2.2.3. Placebo control

Recommendations: 1. Treatments used for TH prophylaxis should be compared with **placebo**. 2. When two presumably active treatments 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 the purpose of the trial is to demonstrate this, there is no need to include placebo.

Comments: The placebo effect in migraine prophylaxis is usually in the range 20–40%, and there is no reason to believe that it is any different in chronic TH (4). Any treatment should be demonstrated to be superior to placebo by simultaneously measuring placebo effect. That two presumably active drugs are found equally effective in a trial is no proof of the efficacy of either if this is not done. To refer to the efficacy of the established drug in previous 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 to be superior to a standard drug, however, the standard drug takes precedence over placebo which, in this case, is not needed; but this may not be known beforehand.

2.2.4. Crossover/parallel design

Recommendations: **Both** crossover and parallel designs may be used in certain situations.

Comments: There are at present no objective data in TH (e.g. on period or carry-over effects) that may validly determine the choice between the two designs. The available information that can be used for discussion stems from migraine trials. The *advantage of the crossover* designs is that it is approximately eight times more powerful than thenon-crossover design in prophylactic trials (29). For certain non-crossover designs, however, the number of patients required is no more than two to four times that required in a crossover design (30) (for further discussion, see 31). The *drawbacks of the crossover* design include the possibility of a carry-over effect, the need for a long total period of treatment (extended by washout periods) which may cause problems with drop-outs, the possibility of having to switch a

patient happily established on an active treatment to placebo, or from placebo to which he has responded to active drug treatment that is no longer indicated, and that side effects can more easily impair blinding. A period effect need not be a problem in the crossover design because suitable statistical techniques can deal with it (28).

When a drug is compared with placebo or an inferior drug, either design can be used if a carry-over effect is not present. If there are indications from previous trials of a carry-over effect, thenon-crossover design should be used.

When comparing two drugs and placebo, the three-way crossover design can be used. This design, if properly performed, is not invalidated by a possible carry-over effect (29) and will result in narrow confidence intervals.

2.2.5. Stratification

Stratification is **not necessary** if strictly diagnosed TH patients are included, and ETH and CTH are kept apart. Stratification is mandatory, however, if patients without and with analgesic misuse (fourth-digit code 8) are recruited. In the future, stratification could become necessary if different subtypes of chronic TH are recognized on clinical or pathophysiological grounds.

2.2.6. Baseline recording

Recommendations: **A 1-month prospective** baseline should be used.

Comments: The use of placebo during baseline is optional but not recommended, especially when a placebo treatment period is included at later stages of the trial. If it is included, placebo responders can often be identified prior to randomization, and either excluded or maintained on placebo for observation of longer-term effects.

2.2.7. 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 accrues gradually (i.e. are needed some weeks before it becomes fully established). Furthermore, and most importantly, only effects of sufficient duration are clinically relevant. For some drugs with long equilibration half-lives (32) longer treatment periods of 4–5 months may be necessary before the potential efficacy is demonstrated. Consideration should be given to observing outcome over even longer periods, and after cessation of treatment, either for carry-over of beneficial effect or for occurrence of withdrawal or rebound symptoms (see Introduction).

2.2.8. Washout periods

Recommendations: In crossover trials a washout period of **1 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 duration must exceed the time taken to eliminate both the drug and its effect, the latter often being unknown. A washout period of 1 month is recommended as a practically feasible compromise, but analysis must look specifically for the possibility of carry-over effect of one or the other treatment, and either demonstrate its absence or make due allowance for it.

2.2.9. Dosage

Recommendations: In assessing any new drug in TH prophylaxis, no assumptions should be made regarding dosage, and attempts should be made to test **as wide a range as possible** in one or more trials.

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

Another no less important problem is the choice of dose in comparative trials. Since information about dose–effect relations in TH prophylaxis is lacking, there is no scientific solution to the problem. Instead good clinical judgement has to be used. There is no justification for deliberate use of a subtherapeutic dose of a standard treatment: placebo should be used instead.

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, or with multiple treatment arms in one trial. In any trial, allowance for dose reduction in the event of intolerance should be considered.

2.2.10. Symptomatic treatment

Recommendations: Patients should use their **usual symptomatic treatment** for acute TH.

Comments: In some previous trials, symptomatic treatment of TH has been regulated, but this instead of the preferred medication will probably not be effective in all cases. Many patients have found by trial and error which symptomatic treatment brings most relief for them, and it is unreasonable to ask such patients

to abstain from this treatment over prolonged periods. If possible, however, one symptomatic treatment should be maintained by each recruited patient. Throughout the trial, change in the amount of symptomatic medication taken can then be used as an index of efficacy of the prophylactic therapy, even if different medications are taken by different patients (see 2.3.2.6). In cases where patients are clearly using ineffective drugs or drug combinations for symptomatic treatment, the investigator should prescribe the most suitable acute treatment.

Where trials are being conducted in CTH, it has to be remembered that use of symptomatic medication on more than 15 days per month should exclude patients from participation.

2.2.11. Control visits

Recommendations: Patients should be seen **every 4th week**.

Comments: Relatively frequent control visits are important for checking the headache diary, observing, recording and treating side effects, altering management where necessary, and otherwise encouraging the patient's continuation in the trial.

2.3. Evaluation of results

2.3.1. Headache diary

Recommendations: The evaluation of efficacy should be based on a **headache diary**.

Comments: The headache diary should be suitable for evaluating the effect parameters chosen from those given below. Secondary interpretation by investigators, i.e. an investigator's evaluation of efficacy, is not recommended. The details of diary design are a local issue, but simplicity is recommended above all.

2.3.2. Effect measures

2.3.2.1. Number of days with headache

Recommendations: Number of **days with headache per 4 weeks** can be used as a primary effect measure.

Comments: This parameter, which allows the use of a more simple headache diary where the patient can indicate for each day whether or not a headache was present, will probably be most useful in large-scale long-term pragmatic trials. Patients can also indicate migraine attacks in the same diary.
It seems from previous trials (4) that this parameter is not very sensitive, taking only limited account of headache duration, but probably clinically the most relevant one.

2.3.2.2. Headache severity

Recommendations: Severity of the headache should be noted by the patient on a categoric **verbal rating scale (VRS)** (0=no

headache; 1=mild; 2=moderate; 3=severe headache) *and/or* on a *visual analogue scale (VAS)* (e.g. 100 mm with "none" and "very severe" at either end) (see 1.3.2.1).

Comments: For general comments, see section 1.3.2.1. Furthermore, in prophylactic trials the patient is asked to rate (in a single value) severity of a headache which at times may be mild and perhaps at others severe, by "*integrating severity over time*". It is difficult to give simple or standardized rules for patients to use. One has to be aware that many but not necessarily all patients are probably rating the maximum severity of the headache. Furthermore, symptomatic (analgesic) treatment may modify severity independently of the trial drug (see 2.3.6). Severity of headache should not therefore be used as a primary parameter of efficacy.

2.3.2.3. Headache relief

Recommendations: The patient is asked to assess not only the initial severity of the condition (recurrent headache as opposed to an episode of headache), but also the degree of relief from it during treatment, and arrive at a difference. A **categoric scale** is recommended (0=no relief; 1=a little relief; 2=some relief; 3=a lot of relief; 4=complete relief) (see 1.3.2.2).

Comments: Scoring relief is highly subjective, but may be a more sensitive way of assessing treatment effects in TH. It is probably more useful in CTH than in ETH, especially when the headache is initially (almost) permanent.

2.3.2.4. Headache duration

Recommendations: Patients should be asked to **record time of start and time of end** of headache episodes (in their view only) as raw data.

Comments: Because many patients with CTH suffer headaches throughout the day, a reduction of a few hours in headache duration may become statistically significant (33). However, the clinical relevance of such a reduction is questionable. Furthermore, duration of headache is modified by acute treatment, which is difficult to standardize among patients. Measurement of duration may be difficult because of uncertainties relating to time of onset, time of offset and interaction of sleep. Duration of headache should therefore not be chosen as a primary efficacy parameter.

2.3.2.5. Headache index

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

Comments: Conceivably the headache indices (I=frequency× severity and II=frequency×severity×duration) reflect the total

suffering of patients. There are, however, considerable problems with both severity and duration (see comments under 2.3.2.2 and 2.3.2.4) and, in headache indices, faulty weighting in the arbitrary numerical severity score is increased by multiplication. The sum of headache frequency (mean monthly number of headache days) and headache intensity (mean monthly severity on VRS/VAS scales) represents an alternative index avoiding multiplication but not the problem of weighting of two different numerical scores. Most importantly, headache indices cannot legitimately be compared between subjects, and any change in a headache index is difficult to attach clinical meaning to.

2.3.2.6. Drug consumption for symptomatic treatment

Recommendations: 1. The number of **headache days** per 4 weeks on which **symptomatic treatment** was taken should be recorded. 2. The **number of tablets per 4 weeks** should be recorded.

Comments: It is difficult to standardize the symptomatic treatment used by patients during a prophylactic drug trial (see 2.2.10). There is no satisfactory way of quantifying the consumption of symptomatic medication in relation to different drugs used by different patients. Thus only the simple qualitative aspect of whether or not a symptomatic treatment was taken for a headache can be used, but this parameter has little value in comparisons between patients. In comparisons of different periods in the same patient, change in drug consumption can be used as a secondary effect parameter.

2.3.2.7. Patients' preferences

Recommendations: The use of patients' preferences is not recommended.

Comments: Patients' preferences for one or the other treatment can only be considered in crossover trials. This can endanger the blinding of patients since the design of the study has to be disclosed.

2.3.3. Efficacy parameters

2.3.3.1. Change in headache days per 4 weeks

2.3.3.2. Change in mean 4-week-severity scores

2.3.3.3. Mean 4-week-headache relief scores

2.3.3.4. Change in mean headache duration per day

2.3.3.5. Change in number of standard doses of symptomatic drugs (analgesics) or days with analgesic intake per 4 weeks.

Comments: There are at present no scientific data pointing directly at one of the preceding as the primary efficacy parameter. However, available clinical experience (4, 33) suggests that 2.3.3.1

could be the most useful in CTH. Although 2.3.3.2 and 2.3.3.4 seem better adapted for ETH, neither severity nor duration of headache is recommended as a primary efficacy parameter (see 2.3.2.2 and 2.3.2.4). Consequently, 2.3.3.1 may be most useful for ETH also. Up to now there is no published experience with relief scores in prophylactic TH trials; these will probably be of value in CTH.

2.3.4. Other outcome evaluations

2.3.4.1. Responder rate (50% effect)

Recommendations: Responders can be defined as those patients with more than 50% reduction in headache days or in headache duration per day during treatment compared with the baseline period. Alternatively, time series analysis (34, 35) can be used in defining responders.

Comments: The choice of a quantal measure of effect of more than 50% reduction is traditional and arbitrary (17), and the investigator should be the judge of what should be considered a good response. This parameter is insensitive but of clear meaning clinically, and can probably be used as a way of retrospectively identifying subgroups of responders. Such a retrospective analysis ought then to be confirmed in prospective trials with this subgroup as the main target. Use of this index can thus, in most trials, only be considered as a hypothesis-generating exercise. Generalization of results of this sort (proportion of responders) is particularly problematic in view of the preselected nature of populations in a trial.

Another probably more reliable way of evaluating responders is to calculate a ''*reliability of change (RC)*'' index (36) according to the following formula: $RC = X_{2-X1/Sdiff}$, where X_1 represents a patient's pretreatment score, X_2 the same patient's post-treatment score, and S_{diff} the standard error of the difference between the two scores calculated from the whole patient group. The value of *RC* indices depends on the measures that are selected to quantify change. The advantages and limitations of the *RC* index have been discussed elsewhere (see 36). In theory, values of *RC* that exceed 1.96 are unlikely to occur ($p < 0.05$) unless an actual change in scores occurs between pretreatment and post-treatment assessment; in other words, changes that exceed this magnitude can be considered as reflecting more than the normal fluctuations on repeated testing with a measure of imperfect reliability. In this way, the proportion of patients who have a major, thus probably clinically meaningful, change can be calculated.

2.3.4.2. Headache impact

Recommendations: The extent to which a patient's life is altered by headache should be measured, if possible.

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Comments: In CTH, as in other chronic pain states, the problem of the clinical versus the statistical significance of treatment outcome has to be taken into consideration (see 9 for a review). As mentioned previously, some studies have reported statistically significant reductions in headache intensity or duration that may not be clinically significant (i.e. real, but not clinically worthwhile) or that may not be treatment-related (i.e. produced merely by the variability of effect measures). Furthermore, there is no simple correlation between pain severity and disability (see 24). There is at present no simple way of overcoming these problems. Potential solutions are offered by evaluations of treatment restorations of adequate or acceptable levels of functioning (quality of life). As already mentioned, Headache Impact Questionnaires have been designed, and partly validated in population-based studies, in order to assess the consequences of headache on professional and social life (19). As soon as their value has been confirmed in clinical settings, their use in TH trials should be recommended.

2.4. Statistics

Calculations of sample sizes in prophylactic crossover and non-crossover trials, based on frequency of attacks, have been published in migraine (37). Repeated analysis (29) of the relative power of the crossover vs the non-crossover design has established an argument that the former is eight times more powerful than the latter in detecting a certain effect. For practical purposes, one can detect an important difference with either design.

In crossover and non-crossover designs, comparisons between groups can be made either of illness during all or the latter part of the treatment periods, or of changes in illness from baseline. The latter is conceivably more powerful, but analyses have so far shown only a marginal gain in power (29). In non-crossover trials the use of the baseline value as a covariate should also be examined. Suitable statistical methods (28) can be used in the crossover design for correction for a period effect ("time effect"), which should always be looked for.

Confidence intervals for differences are recommended (25) as a means of informing the reader fully of the results of the trial. Stating that two treatments are comparable without giving confidence intervals is unacceptable.

3. Trials dealing with non-pharmacological treatments

Non-pharmacological trials in TH should be comparable with the standards required for drug trials and may follow similar, though adapted, recommendations. Experience of such trials is needed.

4. CHECKLISTS (section numbers refer to numbers in the main text)

4.1. ACUTE TREATMENT OF TENSION-TYPE HEADACHE

1.1. Selection of patients

1.1.1.	Diagnostic criteria	Use definitions and diagnostic criteria of IHS
1.1.2.	Associated migraine attacks	Permitted if well recognized by the patient; frequency ≤ 1/month
1.1.3.	Duration of headache	≥ 4 h
1.1.4.	Frequency of headache	≥ 2/month
1.1.5.	Duration since onset	≥ 1 year
1.1.6.	Duration of observation	3-month retrospective and/or 1-month prospective recording
1.1.7.	Age at onset	< 50 years
1.1.8.	Age at entry	18 to 65 years
1.1.9.	Sex	Both female and male patients
1.1.10.	Concomitant drug use	See text (if possible, none)

1.2. Trial design

1.2.1.	Blinding	Use double-blind technique
1.2.2.	Randomization	Essential
1.2.3.	Placebo control	Recommended; see text and ethical considerations
1.2.4.	Crossover/parallel design	Use either design; see text
1.2.5.	Stratification	Not necessary at present
1.2.6.	Dosage	Use as wide a range of doses as possible; establish minimum effect
1.2.7.	Route of administration	Any, as appropriate to the drug
1.2.8.	Timing of administration	When headache intensity is at least moderate
1.2.9.	Number of headaches treated	1 or 2 separated by at least 48 h with the same treatment
1.2.10.	Escape medication	Must be allowed, usually after ≥ 2 h
1.2.11.	Repeated dose studies and long-term trials	See text

1.3. Evaluation of results

1.3.1.	Headache diary	Use a simple report form
1.3.2.	Effect measures	Conform to FDA guidelines
1.3.2.1.	*Headache severity*	VAS *and/or* categorical scale
1.3.2.2.	*Headache relief*	Categorical scale
1.3.2.3.	*Global evaluation of treatment*	*Simple verbal scale*
1.3.3.	*Efficacy parameters*	*Conform to FDA guidelines*
1.3.3.1.	*Number of headaches resolved at 2 h*	
1.3.3.2.	*Headache intensity differences resolved at 2 h*	
1.3.3.3.	*Headache relief (HER)*	
1.3.3.4.	*Use of escape medication*	
1.3.3.5.	*Area under the time-response curve (SHID, TOTHER)*	
1.3.3.6.	*Comparative global evaluation*	

1.4. Statistics

Calculations of sample size	Use primary efficacy parameter; see text
Confidence intervals	Are recommended

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4.2.   **PROPHYLACTIC TREATMENT**

2.1.   **Selection of patients**

2.1.1.	Diagnostic criteria	Use definitions and diagnostic criteria of IHS
2.1.2.	Associated migraine attacks	Permitted if well recognized by the patient; frequency $\leqslant 1$/month
2.1.3.	Duration of headache	$\geqslant 4$ h
2.1.4.	Frequency of headache	ETH: $\geqslant 2$/month; $\leqslant 15$/month; CTH: $\geqslant 15$/month
2.1.5.	Duration since onset	$\geqslant 1$ year
2.1.6.	Duration of observation	3 months retrospective and/or 1 month prospective recording
2.1.7.	Age at onset	<50 years
2.1.8.	Age at entry	18 to 65 years
2.1.9.	Sex	Both female and male patients
2.1.10.	Concomitant drug use	See text

2.2.   **Trial design**

2.2.1.	Blinding	Use double blind technique
2.2.2.	Randomization	Randomize in small blocks
2.2.3.	Placebo control	Recommended; see text and ethical considerations
2.2.4.	Crossover/parallel design	Use either design; see text
2.2.5.	Stratification	Stratify if patients with analgesic misuse are included, which in principle is not recommended
2.2.6.	Baseline recording	1-month prospective baseline
2.2.7.	Duration of treatment periods	At least 3 months
2.2.8.	Washout periods	1 month in crossover trials
2.2.9.	Dosage	Use as wide a range of doses as possible
2.2.10.	Symptomatic treatment	Keep usual treatment constant for each patient during the trial
2.2.11.	Control visits	Every 4th week

2.3.   **Evaluation of results**

2.3.1.	Headache diary	Recommended, keep simple
2.3.2.	Effect measures	
2.3.2.1.	*Number of days with headache*	Should be the main efficacy parameter; see text
2.3.2.2.	*Headache severity*	4-point verbal scale *and/or* VAS; secondary efficacy parameter
2.3.2.3.	*Headache relief*	5-point verbal scale
2.3.2.4.	*Headache duration*	Should be recorded; secondary efficacy parameter
2.3.2.5.	*Headache index*	Not recommended; see text
2.3.2.6.	*Drug consumption for symptomatic treatment*	Should be recorded; see text
2.3.2.7.	*Patients' preferences*	Not recommended
2.3.3.	Efficacy parameters	
2.3.3.1.	*Change in headache days per 4 weeks*	
2.3.3.2.	*Change in mean 4-week severity scores*	
2.3.3.3.	*Mean 4-week-headache relief scores*	
2.3.3.4.	*Change in mean headache duration per day*	

2.3.3.5.	*Change in number of standard doses of symptomatic drugs*	
2.3.4.	Other outcome evaluations	
2.3.4.1.	*Responder rate (50% effect)*	Can be hypothesis-generating; ''reliability of change'' index can be used; see text
2.3.4.2.	*Headache impact*	Should be used as soon as valid instruments become available
2.4.	**Statistics**	
	Sample size calculations	Use frequency of headache; see text
	Confidence intervals	Recommended
4.3.	**NON-PHARMACOLOGICAL TREATMENTS**	
	Should meet comparable standards	

Note: Only practical experience from future trials evaluated methodologically can lead to better guidelines. Investigators in the field are therefore invited to criticize or comment on this first edition. Please write to:

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