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Guidelines for controlled trials of drugs in tension-type headache: Second edition

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Abstract

The Clinical Trials Subcommittee of the International Headache Society published its first edition of the guidelines on controlled trials of drugs in tension-type headache in 1995. These aimed 'to improve the quality of controlled clinical trials in tension-type headache', because 'good quality controlled trials are the only way to convincingly demonstrate the efficacy of a drug, and form the basis for international agreement on drug therapy'. The Committee published similar guidelines for clinical trials in migraine and cluster headache. Since 1995 several studies on the treatment of episodic and chronic tension-type headache have been published, providing new information on trial methodology for this disorder. Furthermore, the classification of the headaches, including tension-type headache, has been revised. These developments support the need for also revising the guidelines for drug treatments in tension-type headache. These Guidelines are intended to assist in the design of well-controlled clinical trials in tension-type headache.

Keywords

Tension-type headache, clinical trials, acute treatment, prophylactic treatment

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Introduction

The Clinical Trials Subcommittee of the International Headache Society (IHS) published its first edition of the guidelines on controlled trials of drugs in tension-type headache (TTH) in 1995 (1). These aimed 'to improve the quality of controlled clinical trials in TTH', because 'good quality controlled trials are the only way to convincingly demonstrate the efficacy of a drug, and form the basis for international agreement on drug therapy'. The Committee has published similar guidelines for clinical trials in migraine (2–4) and cluster headache (5). Since 1995 several studies on the treatment of episodic (ETTH) and chronic TTH (CTTH) have been published, providing new information on trial methodology for this disorder. Furthermore, the classification of the headaches, including TTH, has been revised (6). These developments support the need for also revising the guidelines for drug treatments in TTH.

For discussion of issues applying to clinical trials in general the reader should consult general works on clinical trial methodology (7–10). Only issues of specific relevance to TTH are taken into account here.

In general, non-pharmacological management should always be considered in TTH (11). When it comes to pharmacological management, the general rule is that patients with ETTH (6) are treated with symptomatic (acute) drugs, whereas prophylactic drugs should be considered in patients with CTTH (6) and in patients with very frequent ETTH. Analgesics are often ineffective in patients with CTTH. Furthermore, their frequent use produces risk of toxicity (e.g. kidney and liver problems), as well as of medication overuse headache (12). Naturally, trials of acute and prophylactic therapy have different designs. Accordingly, the guidelines have separate sections for each, comprising the following subsections: patient selection, trial design and evaluation of results. At the end, checklists for both acute and prophylactic trials treatments are given. Suggestions on the various points are given, but only a few are firm recommendations, and none should be regarded as dogmatic. The subcommittee believes, and the comments sections

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indicate, that various different solutions to specific problems may be equally appropriate.

Special clinical features

The TTH is classified into three subtypes according to headache frequency: infrequent ETTH (< 1 day of headache per month), frequent ETTH (1–14 days of headache per month) and CTTH (≥ 15 days per month) (6). This division may seem artificial, but has proved to be highly relevant for several reasons. First, impact on quality of life differs considerably between the subtypes. A person having headache every day from the time of waking, persisting until bedtime, month in and month out, is very significantly disabled. At the other extreme, a mild headache once every other month has very little impact on health or functional ability and needs little if any medical attention. Second, the pathophysiological mechanisms may differ significantly between the subtypes; peripheral mechanisms are probably more important in ETTH, whereas central pain mechanisms are pivotal in CTTH (13) (which may explain why these patients are often difficult to treat). Third, treatment differs between the subtypes, with symptomatic and prophylactic treatments being more appropriate for ETTH and CTTH, respectively. Therefore, as for other headache disorders, a precise diagnosis is mandatory as a prelude to any therapeutic trial of TTH and should be established by means of a headache diary (14) completed for at least 4 weeks.

The classification separates TTH patients with and without disorder of pericranial muscles based on tenderness on manual palpation (6). So far it is unclear whether this has any influence on the response to drug treatment (15), and the subcommittee recommends that this is studied further. Patients with CTTH may have a large intake of analgesics, and it is therefore important to exclude medication overuse headache (12). The intensity of pain in TTH is generally less severe than in migraine, and typically there are no disabling accompanying symptoms. The degree of amelioration produced by effective therapy is thus less pronounced, suggesting that more sensitive measures of efficacy could be useful in TTH. Poor compliance with prophylactic treatment may be a problem in CTTH as it is in migraine (16).

1. Drug trials dealing with the acute treatment of TTH

1.1 Selection of patients (see also 4.1, 4.2 and 4.3)

1.1.1 TTH definition

Recommendations: The diagnostic criteria should conform to the second edition of the International Classification of Headache Disorders (ICHD-II) (6). Separate clinical trials for ETTH and CTTH are recommended (ETTH and CTTH should not be studied in the same trial).

Comments: Although the nosological borders of TTH are still vague, the present ICHD-II criteria should be strictly adhered to. In clinical practice, some people have a TTH-like phenotype without strictly meeting IHS criteria but, nevertheless, are diagnosed as TTH and, if treated accordingly, respond appropriately. Nonetheless, for clinical drug trials, requirements are to be more rigid in order to guarantee reproducibility and a high level of evidence.

1.1.2 Concomitant migraine

Recommendations: Migraine attacks are allowed if they are well recognized by the patient, and if the patient can differentiate between TTH and migraine. The frequency of migraine must not exceed a mean of one attack per month during the preceding year. Furthermore, no more than one migraine attack should be identified, through headache calendars, in the baseline phase of the trial.

Comments: It may be difficult to differentiate between mild migraine without aura and ETTH. A diagnostic headache diary (14) should be used. Since it can be difficult to distinguish between mild migraine and TTH, trials should exclude patients with frequent migraine attacks. This justifies our recommendation that patients with more than one migraine attack per 4 weeks should not be included. More strict appendix criteria for TTH were published in the ICHD-II with the aim of excluding migraine patients (6). The lower sensitivity of the appendix criteria makes them impractical for general use in trials. Moreover, it would be difficult to apply the results of a trial following the strict appendix criteria to normal clinical practice.

1.1.3 Duration of headache

Recommendations: Although the ICHD-II diagnostic criteria allow for a shorter duration, it is recommended in clinical trials that only patients who usually have headache episodes with a duration of ≥ 4 h (if untreated) should be selected in order to avoid uncertainty of distinction from spontaneous resolution and decreasing the statistical power for comparative analyses.

1.1.4 Days with headache

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

1.1.5 Duration of disease

Recommendations: The onset of TTH should have happened > 1 year before the inclusion (TTH should be present for at least 1 year).

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

1.1.6 Duration of observation

Recommendations: There should be a 3-month self-reported retrospective history of the disorder being studied (ETTH or CTTH), and a 1-month prospective baseline recording, preferably by use of a headache diary (14), in order to confirm eligibility.

1.1.7 Age at onset

Recommendations: The onset of TTH should have happened before the age of 50 years.

Comments: TTH beginning after the age of 50 is rare and headache onset in these years is often due to underlying organic disease that sometimes mimics TTH. Few patients will be excluded by this limitation (17).

1.1.8 Age at entry

Recommendations: Patients may be entered into adult studies if they are between 18 and 65 years of age. If children or adolescents or elderly populations are investigated, this should be done in separate trials with proper justification and safety measures.

Comments: Drug development programmes may at some point wish to include both younger and older patients. Special protocols will be required for children and adolescents or the elderly in order to show efficacy as well as safety. Children and adolescents have a much higher placebo rate than adults. Therefore they should be investigated in dedicated separate trials. Special protocols are also needed for subjects > 65 years old. Because they are subject to cerebrovascular disease and other illnesses that increase the hazard in using experimental drugs, older patients should not be included until safety has been shown in younger adults. See special comments 4.3.

1.1.9 Gender

Recommendations: Both women and men should be included.

Comments: The prevalence of TTH is slightly higher in women than in men in the population. In many trials, however, this female preponderance is exaggerated. Efforts should be made, therefore, to recruit men to an extent that reflects its epidemiological prevalence (18–21). In studies of women, precautions should be taken to avoid treating those who may be pregnant or lactating, unless this is the purpose of the study and the proper safety measures are taken.

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. Other concomitant therapies, specifically allowed or restricted, should be specified. In Phase IIa trials, patients should take no other drugs. In later trials (Phase IIb onwards), contraceptive drugs and drugs used for other purposes may be specifically permitted with due precautions if the earlier developmental phases did not suggest a high potential for drug interactions.

Excluded are patients using, over the previous 3 months, other medications that are likely, on available evidence, to affect the disorder being studied, including those who use drugs excessively for headache (e.g. those who regularly take medication for acute headache on ≥ 10 days per month (6)); patients who abuse alcohol or other drugs [Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria (22)]; patients who are allergic or have shown hypersensitivity to compounds similar to the trial drug; potentially fertile and sexually active women who do not practise an acceptable form of contraception.

Comments: Evaluating potential for drug interaction is an important aspect of drug development prior to marketing. Herein, safety of participants is the primary concern, but drug interaction may also obscure treatment effect or its measurement. To exclude patients who occasionally use a sedative or minor tranquillizer is not sensible in later trials, neither is exclusion of women who experience no difficulty using contraceptive drugs. Both would too severely limit the population from which recruits may be drawn, and these are groups of patients who will seek to use a marketed TTH therapy. On the other hand, it is desirable to eliminate patients who take excessive drugs for the treatment of acute headache, because pathophysiology and response to treatment are likely to be altered, and those who abuse drugs or alcohol. People who are known to be resistant generally to headache drugs may unfairly bias the study if preferentially selected, which may happen because of their availability unless they are specifically excluded.

1.1.11 Concomitant diseases

Recommendations: Patients suffering from psychiatric diseases that require treatment, patients suffering

from significant cognitive disorders and patients suffering from other significant chronic pain disorders should be excluded.

Comments: Pain thresholds may be impaired in psychiatric diseases, which should anyway be treated if necessary. Ability to comply with treatment and/or evaluation may be impaired by cognitive disorders.

1.2 Trial design

1.2.1 Blinding

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

Comments: Drugs used for acute treatment of TTH can be reliably evaluated only in randomized, double-blind, clinical trials. Clinical observations or open trials may, however, be the impetus for conducting randomized clinical trials (RCTs).

1.2.2 Placebo control

Recommendations: Drugs used for the acute treatment of TTH should be compared with placebo. When two presumably active drugs are compared, placebo control should also be included in order to test the reactivity of the patient sample.

Comments: The placebo effect in the treatment of TTH is substantial. For example, Steiner et al. reported a placebo-response rate (subjective pain relief 2 h after treatment) of 55% (23). Active drugs should therefore be demonstrated to be superior to placebo. Demonstration that a standard drug and a novel comparator agent do not significantly differ in a trial does not prove that the novel agent is effective (24). Referring to historical controls for the active comparator is not a substitute for a contemporaneous placebo control group. Because patients are permitted to take rescue medication 2 h after intake of study medication, placebo poses no ethical concern.

1.2.3 Parallel-groups and crossover designs

Recommendations: Both parallel-groups and crossover designs may be used.

Comments: The parallel-groups design has the advantage of simplicity. The crossover design is more powerful than the parallel design (25). 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. With a crossover design a period effect may occur and should be accounted for by the analyses. The crossover design allows robust estimates of intra-individual consistency of response using placebo–control groups. In addition, it allows assessments by the patients of the benefit/tolerability ratio by asking for their preference between treatments.

1.2.4 Randomization

Recommendations: Patients should be randomized. Randomization should occur at entry to the trial period, after the baseline prospective assessment.

Comments: True randomization is crucial to avoid bias and, in large trials, contribute to group matching.

1.2.5 Stratification

Recommendations: If patients with a wide range of headache frequencies are included we recommend stratification for frequency.

Comments: Stratification is recommended because there is likely to be a pathophysiological spectrum between peripheral and central mechanisms (26). In future trials, stratification could become relevant according to other factors, e.g. degree of muscle tenderness.

1.2.6 Dose–response curves and dosage

Recommendations: (i) In assessing a new drug for acute treatment of TTH the dose–response curve should be defined in RCTs. The minimum effective dose and the optimum dose(s) (based on both efficacy and tolerability) should be determined. (ii) In comparative RCTs, appropriate doses of each active comparator should be used. If these are not the clinically recommended dose(s), explanation must be given.

Comments: Determining dose in trials comparing two active drugs is difficult, since information about dose–effect relationship in TTH treatment is often lacking. There is presently no scientific solution to this problem. Instead, clinical judgment may be required, and should be justified by appropriate argument.

1.2.7 Route of administration

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

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

1.2.8 Time of administration

Recommendations: Patients should usually be instructed to take the drug as soon as they feel the need to treat.

Comments: It is contrary to clinical practice to delay treatment. It is unfair to patients to ask this. Because patients may not do this when treating themselves routinely, our recommendation mimics a 'real life' approach. Furthermore, delaying treatment until headache is more severe may impair efficacy. On the other hand, treatment of mild pain makes it more difficult to observe beneficial change, and endpoints, as well as power analyses, should account for this.

1.2.9 Number of attacks treated with same treatment

Recommendations: Both in crossover and parallel-groups trials, one or two attacks may be treated with the same drug.

Comments: Repeated intake of the test drug was previously used and recommended (1) as it may be expected to increase the discriminative power of a trial if outcome is averaged across multiple attacks for each patient. However, repeated intake of test medication prolongs the trial considerably, especially in crossover trials, and patients often fail to treat all attacks. Drop-outs may be related to previous lack of efficacy, thereby causing bias. Consistency of response should be evaluated in specially designed RCTs (see 1.2.10).

1.2.10 RCTs evaluating consistency of response

Recommendations: Consistency of response should be evaluated in modified-design crossover RCTs with placebo-control (multiple attacks with random insertion of placebo).

Comments: The optimal number of attacks for such consistency trials in TTH is not known. In migraine, five attacks in a consistency RCT is recommended as a practical compromise (3). Investigators can either include one placebo treatment for all patients, the design recommended above, or, in one group, administer active drug in all attacks. The number of attacks treated with active drug can thus be either four or five. These recommendations are based on experience from migraine trials, since there is limited experience with evaluation of consistency in TTH.

1.2.11 Rescue medication

Recommendations: Rescue medication must be allowed.

Comments: In some cases with parenteral drug administration rescue medication could be used after 60 min, but in most cases with oral administration it is preferable to wait 2 h before rescue medication is allowed. Rescue medication should not be delayed more than 2 h: if rescue is needed then, the trial treatment is unsatisfactory and little is learned by delaying rescue and extending the patient's discomfort.

1.3 Evaluation of results

1.3.1 Timing of observations

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

Comments: The effect on the headache should be scored by the patient at regular time intervals, at least immediately before the use of medication (0 h), and at 1, 2 and 24 h. Shorter time intervals (e.g. 30 min) and shorter total scoring periods can be used, if early effectiveness is expected. Because of the discomfort of the 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. For purpose of familiarization, patients may complete the diary while treating one attack with their usual treatment before inclusion in a trial, or they may complete the diary at the randomization visit recalling their most recent attack. Probably the latter procedure is more acceptable for the patient expecting to try a new trial drug as soon as possible.

1.3.2 Outcome measures

1.3.2.1 Pain-free after 2 h

Recommendations: Pain-free rate at 2 h should be the primary efficacy measure.

Comments: Sustained pain free after 2–24 h is clinically relevant and its rate may alternatively be used as the primary efficacy measure. We suggest that numbers needed to treat (NNT) for pain free at 2 h post treatment be presented.

1.3.2.2 Headache intensity

Recommendations: Intensity of the headache should be noted by the patient on a categorical, 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). Pain intensity difference (PID), e.g. the difference between headache intensity before and 2 h after treatment, could be considered as a secondary efficacy measure.

Comments: Experience with the VAS is limited in TTH trials (27). However, as mentioned above, the pain in TTH is usually mild or moderate. The categorical verbal scale, commonly used for migraine attacks, may thus not be sensitive enough. Sum of pain intensity differences (SPID) could theoretically be useful since it has the advantage of summarizing the benefits of treatment over a clinically relevant period, e.g. 2 h. PID assumes that the pain scale is linear and that a change from severe to moderate headache is equivalent to a change from moderate to mild headache. This has not been analysed so far. These measures are widely used in other pain disorders (28) and have also been used in TTH (29).

1.3.2.3 Disability

Recommendations: Disability, as a measure of functional impairment, could be recorded throughout the observation period as secondary outcome measure.

Comments: Disability is more commonly associated with ETTH than is generally recognized (30). Disability scales take into account the impact of the headache on daily activities. A simple 4-point verbal functional impairment scale can be used, with the terms 'can do everything as usual' (for no disability), 'can do everything, but have difficulties with some activities' (for mild disability), 'can do some things, but not others' (for moderate disability) and 'cannot do anything, or require bed rest' (for severe disability).

1.3.2.4 Rescue medication

Recommendations: The use of rescue medication can be used as a secondary efficacy measure.

1.3.2.5 Global evaluation of medication

Recommendations: A simple verbal scale could be used by the patient: very poor, poor, neutral (neither poor nor good), good, very good. Such scales should always be symmetrical about the neutral point. Global evaluation can be used as a secondary outcome measure.

Comments: This criterion may be one of most clinically relevant, as it takes into account both efficacy and tolerability, the latter excluding its use as the primary efficacy measure. It is probably best used in later trials. It is also useful for comparing active medications.

1.3.2.6 Adverse events

Recommendations: Adverse events should be recorded. Numbers needed to harm (NNH) should be presented.

Comments: Adverse events during treatment should be recorded contemporaneously in the study diary. Spontaneous reports supplemented by responses to open questions are recommended. Adverse events should be rated as mild, moderate, or severe; serious or non-serious; and the time of occurrence and duration should be noted. Serious adverse events must be handled according to regulatory guidelines (31).

Adverse events, which are unwanted effects that occur during treatment, are not necessarily related to treatment. They should be recorded openly in order to detect any unexpected unwanted effects during the development programme of a drug. Investigators can indicate whether they believe that the adverse event was drug-related. It should be noted that regulatory authorities require more detailed reporting of adverse events (31).

1.3.2.7 Patients' preference for treatments

Recommendations: Patients' preference for treatments can be used in crossover trials.

Comments: Benefit/tolerability ratios are difficult to judge from currently performed RCTs. It is unknown how a certain success rate and an incidence of adverse events should be combined into a meaningful expression for the benefit/tolerability ratio. Many patients seem to prefer a more effective drug or dose and will endure the cost of more adverse events if these are relatively transient and mild. In crossover RCTs patients can assess the benefit/tolerability ratios of different drugs or doses by giving their preference for one or other treatment.

1.3.2.8 Consistency of effect

Recommendations: In special crossover design trials comparing active drug and placebo (see 1.2.10) consistency can be defined as treatment success in at least three of four or, better, at least four of five attacks consecutively treated with active drug.

Comments: In RCTs comparing active drug and placebo, two types of multiple attack measures may be reported. Intra-individual consistency (defined above) is the percentage of individuals in a group who respond in a specific number out of a larger number of treated attacks (e.g. four out of five). Population consistency, which may also be of interest, is the proportion of a group who respond in their first, second or *n*'th treated attack. Depending on the design in these RCTs, four or

five attacks are treated consecutively with the same dose of a drug (see 1.2.10) and consistency, defined as above, can be reported.

2. Drug trials dealing with TTH prophylaxis

In general, the subjective nature of TTH and a moderate to high placebo effect (32–40) invalidate open and single-blind trials. However, clinical observation and open studies (e.g. (41)), may be hypothesis-generating for possible prophylactic effect in TTH.

When a possible prophylactic effect in TTH has been suggested by clinical observations or open studies, double-blind, randomized, controlled trials should be performed. In these trials the novel drug should be compared with placebo. Its efficacy relative to an established active comparator should preferably also be evaluated to ensure model sensitivity. The drug should be demonstrated to be better than placebo in at least two separate adequately powered controlled trials. In most past trials comparing two active drugs, these have not been found to be statistically significantly different from each other, even if both are superior to placebo (37, 42–44). However, it is often apparent that the trials are too small to demonstrate comparability. Furthermore, if both drugs are found effective only by comparison with a baseline period, the improvements noted may be due to the natural history of TTH: amelioration may be due to the passage of time and regression to the mean (45). Therefore, comparative trials should also always be placebo controlled.

The numbers of patients needed (see 3) even in cross-over trials may require multicentre trials. If enough patients cannot be recruited it is better to avoid doing underpowered comparative trials, since the results will be unclear and potentially misleading.

As mentioned in the section on evaluation of results, in the planning phase only one or a very few measures should be defined as the primary evaluation measures.

2.1 Selection of patients

2.1.1 TTH definition

Recommendations: The diagnostic criteria should conform to ICHD-II criteria for TTH (6).

Comments: There are people whose symptoms do not meet IHS criteria but, nevertheless, are diagnosed as TTH and, if treated accordingly, respond appropriately. For clinical drug trials, however, requirements should be more rigid than in clinical practice.

2.1.2 Concomitant migraine

Recommendations: Migraine attacks are allowed if they are well recognized by the patient, and if the patient can differentiate between TTH and migraine. The frequency of migraine attacks must not exceed one attack per month during the preceding year.

Comments: It may be difficult to differentiate between mild migraine without aura and ETTH. A diagnostic headache diary (14) should be used. Early safety and efficacy studies should exclude other headache. A precise diagnosis may, however, not be simple, because many patients, in particular those seen in headache clinics, also suffer from migraine. Since it can be difficult to distinguish between mild migraine and TTH, trials should exclude patients with frequent migraine attacks. The subcommittee recommends that patients with more than one migraine attack per 4 weeks are not included. More strict appendix criteria for TTH were published in ICHD-II with the aim of excluding migraine patients (6). The lower sensitivity of the appendix criteria makes them impractical for general use in trials. Moreover, it would be difficult to apply the results of a trial following the strict appendix criteria to normal clinical practice.

2.1.3 Duration of headache (see 1.1.3):
2.1.4 Days with headache

Recommendations: Patients with either frequent ETTH or CTTH can be studied. Inclusion of both types of patients in the same trial is not recommended.

Comments: Prophylactic treatment is generally more relevant for CTTH. Treatment of patients with frequent ETTH may be indicated if the drug has a favourable side-effect profile.

2.1.5 Duration of disease (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 Gender (see 1.1.9):
2.1.10 Concomitant drug use

Recommendations: Appropriate acute therapy must be allowed for individual attacks (see 2.2.10). Patients with medication overuse (46) should be excluded.

Comments: Other concomitant therapy, specifically allowed or restricted, should be specified. In Phase IIa trials, the patient should take no other drugs. In later trials (Phase IIb onwards) contraceptive drugs and other drugs not taken for TTH that may alter metabolism of or are otherwise likely to interact with the experimental drug may be specifically permitted with due precautions.

Excluded are patients taking, or who have taken regularly in the previous 3 months, other medications that are likely, on available evidence, to affect the disorder being studied, including those who use drugs excessively for headache (e.g. those who regularly take medication for acute headache on ≥ 10 days per month (46)); patients who abuse alcohol or other drugs (DSM-IV criteria (22)); patients who are allergic or have shown hypersensitivity to compounds similar to the trial drug; and potentially fertile and sexually active women who do not practise an acceptable form of contraception. Ideally, patients who have taken antipsychotics, antiepileptics, anxiolytics or antidepressants during the previous month should be excluded from preventative trials. However, in Phase III and later trials this may exclude a large subgroup of patients [e.g. users of selective serotonin reuptake inhibitors (SSRIs)] who will be treated with the marketed drug, limiting the relevance of trial results for clinical practice. In such cases, the protocol may be written to include patients on a stable dose of selected agents with no demonstrated efficacy for CTTH, subject to safeguards relating to potential interactions.

Evaluating potential for drug interaction is an important aspect of drug development prior to marketing. In these recommendations, safety of participants is the primary concern, but drug interaction may also obscure treatment effect or its measurement. To exclude patients who occasionally use a sedative or minor tranquillizer is not sensible in later trials, nor is exclusion of women who experience no difficulty using contraceptive drugs. Both would too severely limit the population from which recruits may be drawn, and these are groups of patients who will seek to use a marketed TTH therapy. On the other hand, it is desirable to eliminate patients who take excessive drugs for the treatment of acute headache (because pathophysiology and response to treatment are likely to be altered) and those who abuse drugs or alcohol. People who are known to be resistant generally to headache drugs may unfairly bias the study if preferentially selected, which may happen because of their availability unless they are specifically excluded. However, unresponsiveness to medication may be due to inadequate dose, short duration of trial or other factors. These patients are not unequivocally excluded, but investigators should set clear criteria for their inclusion in the protocol.

A significant proportion of patients with chronic frequent headaches are suffering from medication overuse headache (46). These patients should be withdrawn from excessive analgesic use at least 2 months before inclusion in the study.

2.1.11 Concomitant diseases

Recommendations: Patients suffering from significant affective, psychotic, epileptic, cognitive and other chronic pain disorders should be excluded.

Comments: Exceptions would be trials designed to examine the effectiveness of a drug in subgroups of patients with a specified comorbid disorder: CTTH and comorbid depression, CTTH and comorbid myofascial pain, etc.

Well-established clinical tools, e.g. depression and anxiety scales or the craniomandibular index, should be used when appropriate.

2.2 Trial design

2.2.1 Blinding

Recommendations: Controlled trials in TTH prophylaxis should be double-blind.

Comments: Drugs used for prophylactic treatment of TTH can be reliably evaluated only in randomized, double-blind, clinical trials. Clinical observations may, however, be the impetus for conducting RCTs.

2.2.2 Placebo control

Recommendations: Drugs used for the prophylactic treatment of TTH should be compared with placebo. When two presumably active drugs are compared, placebo control should also be included in order to test the reactivity of the patient sample.

Comments: The placebo effect in TTH prophylaxis has been reported as moderate to high. Bendtsen et al. reported a consistent placebo response in reduction of area-under-the headache-curve of 10–14% in three different studies (32, 38, 39), whereas Holroyd et al. reported a considerably higher placebo response (33). Active drugs should be demonstrated to be superior to placebo. That two presumably active drugs are found equally effective in a trial is no proof of efficacy of either, nor of comparability. To refer to the previous efficacy in other trials of an established drug used as a comparator is not enough; it is using historical controls, a method largely discouraged in medicine. Both drugs should also be shown contemporaneously to be superior to placebo.

2.2.3 Parallel-groups and crossover designs

Recommendations: Either parallel or crossover designs can be used, depending upon the research objectives and drugs under study.

Comments: The advantage of the crossover design is that it is approximately eight times more powerful than

the parallel-groups design in prophylactic migraine trials (47). For certain parallel-groups designs, however, the number of patients required is no more than two to four times the number required in a crossover design (48) (for further discussion see (49)). There are no calculations specifically for TTH. The drawbacks of the crossover design are: (i) the possibility of a carry-over effect; (ii) the need for a long total period of treatment (extended by wash-out periods) with concomitant increases in dropouts and loss of statistical power; (iii) side-effects that can more easily unmask blinding when a patient is exposed to both treatments; and (iv) at the crossover point, those doing well on active drug are not appropriately treated by switching to placebo, those not effectively treated on active drug are not appropriately treated by switching to placebo, those doing well on placebo no longer need active drug and are not appropriately treated by switching to it. A period effect is not a problem in the crossover design, because suitable statistical techniques can deal with it (50).

2.2.4 Randomization

Recommendations: (i) Patients should be randomized in relatively small blocks. (ii) For the triple crossover design (two active drugs vs. placebo) the Latin square method should be used. (iii) Randomization should occur after the run-in (baseline) period.

Comments: Patients are often recruited to prophylactic TTH trials over extended periods. It is therefore preferable to randomize in relatively small blocks (usually four to six patients) because patient selection may vary with time.

2.2.5 Stratification

Recommendations: Stratification is not necessary.

Comments: There are no empirically established prognostic factors within the group who qualify for preventative medication. In the future, stratification could become necessary if different subtypes of TTH are recognized on clinical or pathophysiological grounds. Stratification may be considered, e.g. if patients with concomitant depression or patients taking selected antidepressants (e.g. SSRIs) are included.

2.2.6 Baseline (run-in) period

Recommendations: A 1-month baseline run-in period without placebo is recommended.

Comments: During the baseline run-in period placebo can be given to identify and exclude placebo responders prior to randomization. This is not recommended because (i) it will hinder observation of the true placebo response later in the trial; and (ii) the included sample will no longer be fully representative of the original population.

2.2.7 Duration of treatment periods

Recommendations: In general, treatment periods of at least 12 weeks should be used in parallel-group studies and of at least 8 weeks in crossover studies.

Comments: CTTH tends to be more stable with regard to frequency of headache than migraine, and shorter treatment periods than 3 months can therefore be accepted in cross-over studies to reduce drop-out rates. The efficacy of many drugs accrues gradually (i.e. needs some weeks before becoming fully established), and only effects of sufficient duration are clinically relevant. Longer treatment periods, e.g. ≥ 6 months, are encouraged to reflect likely clinical use.

2.2.8 Wash-out periods

Recommendations: In crossover trials a wash-out period of 1 month should be used.

Comments: With prophylactic drugs the benefits of treatment may persist even after treatment is withdrawn. Since drug effects are often slow in onset and wane gradually, a drug-free (placebo) wash-out 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 wash-out period of 1 month is recommended as a practically feasible compromise. Part of the wash-out period can be used to introduce and up-titrate the drug that will be given in the following treatment period.

2.2.9 Dosage

Recommendations: Attempts should be made to test as wide a range of doses as possible. Usually, the no-effect dose and the maximum tolerated dose should both be established.

Comments: As long as the pharmacological basis for the efficacy of prophylactic drugs in TTH remains unknown, the choice of doses in trials is a purely empirical compromise between observed efficacy and tolerability. The willingness of patients to take the drug for months depends heavily on the ratio between perceived efficacy and side-effects actually experienced. The choice of dose(s) is therefore one of the crucial factors in determining the chances of successful completion of the trial, whilst this compromise tends to induce the use of suboptimal doses in prophylactic TTH trials. So far, no dose–response curve has been established for any drug used in TTH prophylaxis. No less important is the problem of choice of appropriate ('comparable')

doses of two or more active drugs in comparative trials. Since information about dose–effect relationships in TTH prophylaxis is lacking, there is no scientific solution but only good clinical judgement as a way forward.

2.2.10 Symptomatic (acute) treatment

Recommendations: Patients' usual symptomatic treatment should be reviewed prior to trial entry. Provided that there is no element of misuse and provided that it can be safely used with the study medication, patients should continue to take their usual symptomatic treatment unchanged throughout the trial.

Comments: In a few previous trials, symptomatic treatment of attacks has been standardized or otherwise regulated, but in such circumstances is unlikely to be optimal for all patients. Many patients have by trial and error found symptomatic treatment giving some degree of relief, and it is unreasonable to ask patients to abstain from such treatment over prolonged periods.

2.2.11 Control visits

Recommendations: Patients should be monitored at least every fourth week.

Comments: Frequent monitoring is necessary in order to check the headache diary and encourage patients' continuation in the trial and compliance with medication. Ideally, monitoring is by clinical visit, but other methods of contact (e.g. telephone or Internet) may be appropriate.

2.2.12 Compliance monitoring

Recommendations: Compliance with prophylactic medication in clinical trials should be monitored.

Comments: There is evidence that compliance with migraine prophylactic drugs is often poor (16, 51), and their efficacy may be restricted because of this. There is no reason to believe that this should be different in TTH. Clinical trials in which compliance is not monitored may conclude that a drug has no efficacy when it has not actually been taken.

2.3 Evaluation of results

2.3.1 Period of observation

Recommendations: The period used for evaluation should be defined, e.g. the entire treatment period or the last 4 weeks of treatment.

2.3.2 Headache diary

Recommendations: The evaluation of efficacy should be based on a headache diary, which captures the key assessment measures of the study.

Comments: The headache diary should be suitable for evaluating the efficacy and tolerability measures chosen from those recommended below. Patients can also indicate migraine attacks in the same diary.

2.3.3 Outcome measures

2.3.3.1 Days with TTH

Recommendations: Days with TTH per 4 weeks can be the primary efficacy measure.

Comments: The number of TTH days should be recorded irrespective of headache duration. This parameter, which allows the use of a 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. At present there are no conclusive data indicating whether days with TTH or AUC (see below) should be preferred as primary efficacy measure in CTTH. It is recommended that the efficacy measures are presented at regular intervals, e.g. for each week, during the trial as secondary efficacy measures, to give an impression of onset of effect and of possible increased or diminished effect with time.

2.3.3.2 Area-under-the-headache curve

Recommendations: Area-under-the-headache curve (AUC) can be the primary efficacy measure.

Comments: AUC can be calculated as the sum of the daily recordings of headache duration × headache intensity (also called headache index) (39) or as the sum of multiple per day pain intensity recordings (33). AUC seems to be more sensitive than days with headache for trials in CTTH (38, 39). It has been suggested (52, 53) that this should be the primary efficacy parameter rather than days with headache, because it better reflects the total suffering of patients. This is supported by clinical experience indicating that a modest reduction in headache intensity and duration is considered highly relevant and a major improvement for patients with CTTH. However, there are problems with recording for both intensity and duration (see comments under 2.3.3.3 and 2.3.3.4) and, when used in headache indices, faulty weighting in the arbitrary numerical intensity score will be increased by multiplication. When AUC is used as the primary efficacy measure, days with headache should be presented as a secondary efficacy measure. At present there are no conclusive data indicating whether days with TTH or AUC should be preferred as the primary efficacy measure in CTTH.

2.3.3.3 Intensity of headache

Recommendations: Intensity of the headache can be used as a secondary efficacy measure.

Comments: Intensity can be noted by the patient on a categorical VRS or VAS. However, in prophylactic trials the patient is being asked to rate, in a single value, intensity of headache which at some time is mild and perhaps later severe by 'integrating intensity over time'. It is difficult to give simple or standardized rules for patients to use. Investigators should be aware that patients are probably rating the maximum intensity of headache. Either a 4-point VRS (0 = no headache; 1 = mild headache; 2 = moderate headache; 3 = severe headache) or an 11-point numerical scale (0–10, in which 0 indicates headache-free, 5 indicates moderate headache and 10 indicates the worst headache imaginable) (38) can be used. Alternatively, a VAS (e.g. 100 mm with 'none' and 'very severe' at either end) can be used, but may be too complicated in long-lasting prophylactic RCTs. Existing pain ratings are not true interval scales, although they are typically treated as approximate interval scales for analysis. Item response theory (54) and other advances in scale development may lead to interval scale pain ratings with better psychometric properties. Improvements in pain rating scales have the potential to provide more reliable and sensitive outcome measures and thus are encouraged.

2.3.3.4 Duration of headache

Recommendations: Duration of headache can be used as a secondary efficacy measure.

Comments: Patients may be asked to record the number of hours with headache for each day. However, measurement of duration is difficult because of uncertainties relating to time of onset, time of offset and interaction of sleep.

2.3.3.5 Drug consumption for acute treatment

Recommendations: Drug consumption can be used as a secondary efficacy measure.

Comments: (i) The number of headache days treated with acute (symptomatic) treatment should be recorded. (ii) The number of doses should be recorded.

It is neither ethical nor practically feasible to standardize the symptomatic treatment used by 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. For the moment, the simple qualitative record of the number of days a symptomatic treatment is taken can be supplemented by a count of dosage units. This can only be a secondary outcome measure. In within-patient (crossover) comparisons, acute drug consumption may have value. Its use even as a secondary measure is dubious in between-patient comparisons.

2.3.3.6 Patients' preferences

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

Comments: Patients' preferences for one or other treatment 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.

2.3.3.7 Responder rate

Recommendations: (i) Responder rate can be used as a secondary efficacy measure. (ii) NNT for responder rates should be presented.

Comments: Responder rate is defined as the percentage of subjects in a treatment group with at least 50% improvement in the primary efficacy measure during the evaluation period compared with the baseline period. A $\geq 50\%$ reduction is traditionally used in pain trials. However, this is arbitrary, and the investigator (or patient) should be the judge of what is considered a good response. Since CTTH is notoriously difficult to treat and in order to take the placebo effect into account, some investigators have defined responders as the percentage of subjects in a treatment group having a $\geq 30\%$ improvement in the primary efficacy parameter compared with placebo (39).

2.3.3.8 Adverse events

Recommendations: (i) Adverse events during treatment should be recorded. (ii) Numbers needed to harm should be presented.

Comments: Spontaneous reports supplemented by responses to open questions are recommended. Adverse events should be rated as mild, moderate or severe; serious or non-serious; the time of occurrence and duration should be noted; also to be recorded is whether an adverse event led to discontinuation of treatment. Serious adverse events must be handled according to regulatory guidelines.

Adverse events tend to occur before efficacy, and in clinical practice this is a major problem in prophylactic treatment of TTH, often leading to discontinuation of treatment. Incidence of adverse events, especially adverse events leading to discontinuation of treatment, should therefore be regarded as one of the major measures for judging a prophylactic TTH drug.

Nevertheless, adverse events, which are unwanted effects that occur during treatment, are not necessarily related to treatment. They should be recorded openly in order to detect any unexpected unwanted effects during the development programme of a drug. Investigators can indicate whether they believe that the adverse event was drug-related. It should be noted that regulatory authorities require more detailed reporting of adverse events with new drugs (31).

2.3.3.9 Quality of life and disability measures

Recommendations: Quality of life and/or disability recorded throughout the study could be considered as secondary outcome measures.

Comments: As there are no validated scales developed specifically for TTH, we suggest the use of measures developed for assessing the impact of headaches on quality of life, such as the Headache Disability Inventory (55, 56) and the Headache Impact Test or HIT 6 (57). Quality of life instruments that are not headache specific such as the Medical Outcomes Study SF-36 (58, 59) may be less sensitive, but useful as additional measures. See review of psychometric properties of Quality of Life measures for headache (60).

3. Statistics

Recommendations: Sample size has to be calculated and the basis for the calculation should be explicitly reported. Confidence intervals (CIs) should be presented for any outcome measure when applicable. Intention-to-treat analysis is usually preferred as the primary analysis. If a per-protocol analysis is used instead, justification should be given.

Comments: To calculate sample size, the investigator needs to estimate the placebo response and define the clinically significant difference to be detected. Standard statistical methods can be used for analysis of outcome measures in both crossover and parallel-groups trials. CIs for differences between active drug and placebo as well as between two active drugs (61) are recommended in order to inform the reader more fully of the meaning of the results of the trial. A statement that two drugs are comparable without giving CIs is unacceptable.

In the parallel-groups design, comparisons between groups can be made either as direct comparisons during the treatment periods or as comparisons of changes from baseline. The latter is conceivably more powerful, but analyses in migraine have so far shown only that this is marginally so (Tfelt-Hansen, personal observation). In parallel-groups trials the use of the baseline value as a covariate can also be examined, but results of this analysis should be judged with caution (62). Suitable statistical methods (50) can be used in the crossover design for correction for a period effect ('time effect'), if present.

4. Special comments

4.1 Sources of patients

Patients with TTH attending specialist clinics may not be representative of the larger number seen by primary care physicians. Although there is little formal evidence of significant differences between these, recruitment of patients primarily from tertiary headache centres may result in undesirable selection of treatment-refractory patients. Neither group is likely to match those in the general population who do not seek medical advice.

Clinical trials need to recruit widely from the population who will use the drug when marketed. Early (Phase II) TTH trials may be more readily conducted in specialist centres where resources exist to carry them out. In later development, patients should be enrolled from primary care with as few restrictions as possible. If an over-the-counter (OTC) drug is investigated, patients should be recruited from a population that usually treats headache episodes with OTC and not prescription drugs.

4.2 Patients who have already participated in several trials

It is undesirable to include the same patients in trial after trial. From the scientific point of view, patients who make themselves available for multiple trials may not fairly represent the target population.

4.3 Trials in children and adolescents

Few RCTs of drugs for TTH have been performed in children or adolescents (63). There is a great need for further well-controlled studies (63).

5. Publication of results

'Publication of research is an ethical imperative (64). Medical knowledge worldwide is developed in part on the published results of previous research work. Future research properly takes into account all that has been done before. Both are at risk of being misled if publications present only a partial account of past research, especially if the part that is missing is ''selected'' (65).'

Headache treatment, as any other, should be based as far as possible on evidence of efficacy, tolerability and safety in the proposed use. The most reliable

evidence for efficacy and tolerability is from RCTs, and the best evidence is gained by a systematic review of all such trials that have been done. This requires the full results of all such trials to be in the public domain.

This Subcommittee therefore strongly supports one of the firm recommendations of the Ethics Subcommittee of IHS (65): 'As a general rule, every methodologically sound randomized controlled trial should be published (and only such trials should be carried out). Publication should be in such a way as to allow evaluation of the results; publication solely as an abstract or in non-peer reviewed supplements is unacceptable'.

The publication should conform to generally accepted rules for reporting RCTs (http://www.consort-statement.org/) (66) Investigators and sponsors should negotiate time-lines for publication at the outset and ideally they should form part of the protocol.

6. Checklists (numbers refer to those in the main text)

6.1 Acute treatment	
1.1 Selection of patients	
1.1.1 TTH definition	Use ICHD-II
1.1.2 Concomitant migraine	Permitted if attacks are well-recognized by the patient; frequency $\leq$ 1/month
1.1.3 Duration of headache	$\geq$ 4 h
1.1.4 Days with headache	$\geq$ 2/month
1.1.5 Duration of disease	$\geq$ 1/year
1.1.6 Duration of observation	3 months retrospective history and 1 month prospective recording
1.1.7 Age at onset	$<$ 50 years
1.1.8 Age at entry	18–65 years
1.1.9 Gender	Both women and men
1.1.10 Concomitant drug use	See text
1.1.11 Concomitant diseases	See text
1.2 Trial design	
1.2.1 Blinding	Use double-blind technique
1.2.2 Placebo control	Recommended, see text
1.2.3 Parallel-groups/crossover	Use either design, see text
1.2.4 Randomization	Essential
1.2.5 Stratification	See text
1.2.6 Dose–response curve	Should be defined, see text
1.2.7 Route of administration	In early trials use parenteral route, if possible
1.2.8 Time of administration	When treatment is first needed
1.2.9 Number of attacks treated with the same treatment	One or two attacks, see text
1.2.10 Consistency of response	See text
1.2.11 Rescue medication	Allowed, usually after $\geq$ 2 h
1.3 Evaluation of results	
1.3.1 Timing of observations	Use a simple report form, see text
1.3.2.1 Pain free after 2 h	Recommended primary efficacy measure
1.3.2.2 Headache intensity	Secondary efficacy measure
1.3.2.3 Disability	Secondary efficacy measure
1.3.2.4 Rescue medication	Secondary efficacy measure
1.3.2.5 Global evaluation of medication	Secondary efficacy measure
1.3.2.6 Adverse events	Must be recorded, see text
1.3.2.7 Patients' preference for treatments	Secondary efficacy measure
1.3.2.8 Consistency of effect	See text

(continued)

Continued

6.2 Prophylactic treatment	
2.1 Selection of patients	
2.1.1 TTH definition	Use ICHD-II
2.1.2 Concomitant migraine	Permitted if attacks are well-recognized by the patient; frequency $\leq$ 1/month
2.1.3 Duration of headache	$\geq$ 4 h
2.1.4 Days with headache	Frequent episodic TTH or chronic TTH
2.1.5 Duration of disease	$\geq$ 1/year
2.1.6 Duration of observation	3 months retrospective history and 1 month prospective recording
2.1.7 Age at onset	$<$ 50 years
2.1.8 Age at entry	18–65 years
2.1.9 Gender	Both women and men
2.1.10 Concomitant drug use	See text
2.1.11 Concomitant diseases	See text
2.2 Trial design	
2.2.1 Blinding	Use double-blind technique
2.2.2 Placebo control	Recommended, see text
2.2.3 Parallel-groups/crossover	Use either design, see text
2.2.4 Randomization	Randomize in small blocks
2.2.5 Stratification	Not necessary
2.2.6 Baseline recording	One-month prospective baseline
2.2.7 Duration of treatment periods	At least 12 weeks in parallel-groups and at least 8 weeks in crossover studies, see text
2.2.8 Wash-out periods	One month in crossover trials, see text
2.2.9 Dosage	Use as wide a range of doses as possible
2.2.10 Symptomatic treatment	Keep usual treatment constant during the trial
2.2.11 Control visits	At least every 4th week
2.2.12 Compliance monitoring	See text
2.3 Evaluation of results	
2.3.1 Period of observation	See text
2.3.2 Headache diary	Should be used
2.3.3.1 Days with headache	Can be primary efficacy measure
2.3.3.2 Area-under-the-headache curve	Can be primary efficacy measure
2.3.3.3 Intensity of headache	Can be secondary efficacy measure
2.3.3.4 Duration of headache	Can be secondary efficacy measure
2.3.3.5 Drug consumption for acute treatment	Can be secondary efficacy measure
2.3.3.6 Patients' preferences	Not recommended
2.3.3.7 Responder rate	Can be secondary efficacy measure
2.3.3.8 Adverse events	Must be recorded, see text
2.3.3.9 Quality of life and disability measures	Can be secondary efficacy measures
6.3 Statistics	
Sample size	Should be calculated
Confidence intervals	Should be presented
Intention-to-treat analysis	Should be used when possible

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