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Guidelines Update: Guidelines of the International Headache Society for controlled trials of preventive treatment of migraine in children and adolescents, 1st edition – An experience-based update

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Abstract

Background: Recent experience in designing and running clinical trials on new medications for the prevention of migraine in children and adolescents highlighted the need for revision of the 1st edition of the International Headache Society Guidelines for clinical trials of preventive treatment of migraine in children and adolescents which were published in 2019.

Methods: The authors of the 1st edition of the guidelines formed an informal focus group with aims of appraising the performance of the guidelines, clarifying any ambiguity and providing improvements, where needed, based on personal experience and expert analysis.

Results: This review and the following update were able to address issues related to the classification of migraine, the duration of migraine attacks, the age groups of children and adolescents, the use of electronic diaries, the assessment of outcome measures, the need for an interim analysis and the issues related to placebo response.

Conclusions: This update provides necessary clarifications of the guidelines in order to enable better design and running of future clinical trials for the preventive treatment of migraine in children and adolescents.

Keywords

Adolescents, children, clinical trials, migraine, preventative treatment

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Introduction

The 1st edition of the International Headache Society (IHS) Guidelines for clinical trials of preventive treatment of migraine in children and adolescents was published in 2019 (1). Over the past four years, researchers and the pharmaceutical industry have engaged with these guidelines in designing clinical trials, testing the efficacy of new medications for the prevention of migraine attacks in children and adolescents. Some of us, alongside other headache specialists, were actively involved in such trials with several roles, e.g. advisors to the industry, national/international coordinating investigators, or local principal investigators. Active involvement in trials at these levels has drawn our attention to the need for further clarification, amendment, or development of the guidelines in order to allow easy implementation, successful recruitment of patients and appropriate analysis of data.

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The classification of migraine subtypes

The IHS guidelines for clinical trials on migraine treatment are generally comprehensive, inclusive and clear in emphasizing the importance of the use of the criteria of the International Classification of Headache Disorders (ICHD-3) for the diagnosis of migraine and migraine subtypes (2). In ICHD-3, migraine is defined as a headache characterized by episodic attacks with distinct characteristics and associated features. The subcategory of chronic migraine (CM) is included and defined by at least 15 days of headache per month for at least three months. At least eight of these 15 days should be consistent with the diagnosis of migraine. The ICHD-3 does not selectively identify the opposite (i.e., headaches occurring on less than 15 days per month), although an editorial authored in 2020 by the current coordinator of the committee for Headache Classification officially introduced an interim definition of episodic migraine (EM), as a 'headache occurring on less than 15 days a month over the last 3 months, which on some days is migraine' (3).

The distinction between episodic (EM) and chronic migraine (CM) became the basis on which the design of clinical trials is made, creating some degree of confusion in the non-expert audience by defining 'episodic' as a headache manifesting over time with multiple, recurrent episodes. Furthermore, there is little to no biological evidence to sustain the numerical divide, especially in those patients that fluctuate around the 15 days mark. In many of the most recent research studies, participants are, therefore, assigned strictly to either the EM or the CM arms of the trial as if the two groups represented two different diseases and not just a continuum of the same one, with an artificial demarcation. This situation has created many screen failures in trial recruitment, screening and implementation, as patients have to be allocated to one of the two groups and end up being excluded if they fluctuate from one to the other during the screening period.

The Trials Guidelines make it clear that the diagnosis of CM should comply with the latest edition of ICHD. However, the guidelines also contain the following comment: 'Trials can be designed to include or exclude subjects with CM explicitly or to include all subtypes of migraine and pre-plan a sub-analysis of migraine outcomes based on number of headache days per month' (1). The authors of the guidelines seem to have foreseen the potential problems associated with the arbitrary subdivision of migraine into EM and CM on either side of the 15 headache days per month. In the meanwhile, published research has also shown the issue of such fluctuation in a population-based study of adult patients with EM and CM (4). In children migraine attacks were shown to vary in frequency over the year with a lower number of attacks during the school summer holiday (5).

In this context, we feel it is necessary to revisit the guidelines' comment on the diagnosis of migraine subtypes to emphasize the option of recruiting all patients with migraine and to put in place a pre-planned sub-analysis of migraine outcome based on the number of headache days per month during the screening period.

The duration of migraine attack

An additional area of concern is the concept of migraine as a disease characterized by a succession of attacks, not by single attacks. ICHD-3 clearly states that the diagnosis of migraine without aura can be established only after the child/adolescent has had at least five episodes that satisfy the criteria for migraine. This does not require that all the attacks experienced by the patient should bear the migraine features, although many of them will have some degree of migraine features and will respond to standard acute treatment for migraine attacks. As an example, children may experience episodes lasting less than two hours or more than 72 hours, but as long as they have been appropriately diagnosed with migraine without aura, these attacks also represent an expression of the disease – migraine. In other words, not all the attacks/episodes need to satisfy ICHD criteria for migraine. It is important to make it clear when recruiting patients for clinical trials that having episodes outside the usual duration range does not constitute an exclusion criterion as long as the child or adolescent has been properly diagnosed with the disease.

Stratification of age groups

Another issue that requires clarification is the age of entry into trials. The guidelines also commented on the fact that the prevalence of CM in children under the age of 12 years is uncertain and likely much less frequent than adolescents. Thus, recruitment for clinical trials in young children with CM can be unpredictable and prolonged. It is therefore recommended to remove the age division between children 6–11 years of age and adolescents 12–17 years of age and to design trials to include all children 6–17 years of age with a pre-planned sub-analysis of the outcome and safety based on age at recruitment in order to satisfy regulatory authorities' requirement.

Diaries and documentation of migraine attacks

The use of e-diaries can be a conceptionally attractive proposition because of its potential for reliable timing,

entries, and analysis. Due to these theoretical benefits, e-diaries have become the preferred option for pharmaceutical industry giving them control and timely insight on the progress of the screening period and the response to treatment after randomization. As noted in the original guidelines, e-diaries can be a burden on child and family with the requirement for specific times for entering data, dependency on successful transmission and connection to Wi-Fi or the phone network (1). Many of the trials conducted in the past several years have faced issues with e-diaries, with multiple consequences for the patients: delayed treatment, time consuming procedures for filling in complicated e-diaries, sometimes within a restricted time of entry (i.e., only from 6 pm to 11 pm). This, combined with a required minimum percentage of entries and no allowance for delayed entry, has led to the exclusion of patients from trials or to the loss of information. It seems therefore important to consider that in the trials using e-diary as the primary tools for capturing data, the use of a paper diary should be allowed, at least for a limited time, when the e-diary is unavailable or malfunctioning, especially during the screening period and the first 12 weeks following randomization in order to achieve maximum compliance.

Outcome measures

As regards the outcome measures, the use of monthly headache days (MHD) and monthly migraine days (MMD) as outcome measures is simple and easy to measure but may not reflect the true improvement or lack of it. MHD and MMD are blunt instruments because they give equal weight to short migraine episodes lasting less than two hours and long episodes lasting up to 23 hours. Also, MHD and MMD do not distinguish between episodes with mild or severe headaches. Participants may not experience reduction in MHD or MMD, while experiencing a significant reduction in headache durations and/or severity, reduction in other bothersome symptoms such as nausea or vomiting, or reduction in disability. All of these can be clinically relevant indicators that go undetected when using MHD or MMD alone. In a recent publication, adolescents suffering from CM rated the reduction in attack intensity as one of the most valued outcome measure (6). PedMIDAS is a validated and useful tool for the assessment of the impact of migraine on a child's education and social life, but also has the risk of giving equal weight to each one of the six questions (7). Thus, it can be used in association with MMD or MHD with a pre-planned sub-analysis of each question response to capture and refine the overall response to treatment.

MMD itself can be problematic if it requires that each migraine episode has all the features required by the diagnostic criteria for migraine. One of the key principles in the acute treatment of attacks of migraine is early treatment with an effective dose of an acute medication. If a trial does not take into account this possibility, then attacks that are clearly recognized by the participant as a migraine attack and are appropriately treated with an effective acute medication would be entirely missed. It is therefore recommended that if MMD is used, then the attacks recognized as migraine attack by participants and/or treated with an appropriate medication, should also be included in the calculation.

The issue of placebo response

The high placebo response in clinical trials of preventive treatment of migraine in children and adolescents is an issue that needs to be addressed (8). However, it is acknowledged that there is no optimal solution to this problem. Acceptable options to overcome the placebo effect include: a) accepting that the placebo response rate in children and adolescents can be as high as 50% and, as such, trials should aim to recruit a large enough number of participants to achieve the needed statistical power; b) clinical trials may be designed to treat all patients with the active drug for at least three months followed by randomization to placebo or the active drug with analysis taking into account a washout period, c) a carefully designed cross-over trial with same provision of taking into account the washout period before analysis of outcome measures and d) ensuring recruitment of patients cover the whole year in order to avoid the natural drop in number of migraine attacks during the summer months of school holidays (5).

Having scrutinized and weighted the above considerations we suggest the following update to the 1st edition of the International Headache Society Guidelines for clinical trials of preventive treatment of migraine in children and adolescents.

Recommendations

1. The distinction between chronic and episodic migraine for the purpose of clinical trials for the preventive treatment of migraine in children and adolescents may be removed and children with all frequencies of migraine can be recruited with a pre-planned sub-analysis based on the frequency of migraine during the screening period.
2. Trials can recruit children and adolescents between the ages of 6–17 years with pre-planned doses based on body weight and pre-planned sub-analysis into

groups of participants based on their ages at the time of screening period.
3. The adoption of more refined outcome measures capable of capturing improvements in severity and duration as well as frequency of migraine attacks is suggested in association with MHD or MMD. Quality of life assessment tools are also recommended.
4. Pre-planned interim analysis for futility should be part of the trial design.
5. If eDiaries are chosen to collect information, a backup system with a paper diary is recommended.
6. Minimizing the effect of placebo is encouraged by adopting appropriate measures as discussed above.

Declaration of conflicting interests

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