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Chapter 5

What do patients consider to be the most important outcomes for effectiveness studies on migraine treatment? Results of a Delphi study

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ABSTRACT

Background

The outcome measures most frequently used in studies on the effectiveness of migraine treatment are whether the patient is free of pain, nausea, and free of photophobia/phonophobia within two hours. However, no patient-centred outcome measures are available. Therefore, we performed an online Delphi procedure to compile a list of outcome measures deemed most important to migraine patients.

Methods

From a large database of migraine patients, we randomly selected 150 male and 150 female patients. We asked the open-ended question: 'If a new medicine was developed for migraine attacks, what would you wish to be the effect of this medication to be?' In the second and third rounds, we presented the answers of the first round and asked the patients to rate the importance of each item.

Results

The initial response rate was 56% (n=169). In the subsequent rounds the response rates were 90% (n=152), and 97% (n=147), respectively. Patients wanted their attack medication to treat the headache within 30 min, to prevent the attack from getting worse, ensure they could function properly within 1 h, and prevent recurrence of symptoms during the same day.

Conclusions

The currently used outcome measures in migraine research do not sufficiently reflect the wishes of patients. Patients want the medication to work faster, to abolish pain at an earlier stage, to make them able to function properly quickly, and to prevent recurrence. These aspects should be considered in future evaluation of new attack medication for migraine.

INTRODUCTION

The most important outcome measure used in studies on the effectiveness of migraine treatment is whether the patient is pain free within two hours after taking the medicine.[1] This outcome measure is used to assess a new migraine drug for introduction on the market. Other symptoms assessed in this evaluation are nausea/vomiting and photophobia and phonophobia. The choice for these outcome measures is based on consensus among migraine specialists.[1] Despite claims that these outcome measures reflect the expectations of migraine patients, patients' wishes have only been explored by asking their opinion about the currently used outcome measures.[2;3] To our knowledge, migraine patients have not been asked to add what they consider important themselves. Therefore, it can be questioned whether the currently used outcome measures in migraine research sufficiently reflect what is most relevant to the patients.[4]

The importance of outcome measures relevant to patients was the rationale to start a Delphi study. The Delphi consensus method is commonly used within the health and social sciences to determine to what extent people agree about a given issue, or to transform opinion into group consensus. It is an iterative multistage process with a flexible approach.[5;6] In the present study we asked migraine patients to formulate their own outcome measures, with the aim was to compile a short list of outcome measures that they considered most important. A similar project in patients with rheumatoid arthritis led to surprising results and the development of new outcome measures, that are now recommended in drug trials worldwide.[7]

METHODS

We performed a Delphi procedure with web-based questionnaires that allowed patients to give their input over three rounds. This method has previously been used in the development of outcome measures.[8] In the first round we made an inventory of all possible opinions and we compiled a list of candidate items. In the second and third rounds we asked patients to evaluate these items. The aim was to compile a short list of outcome measures that were considered most important by the patients and that physicians might not have considered before. Also, we aimed to establish to what extent patients agree with the commonly used outcome measures.

Patient panel

For this Delphi project, we randomly selected 150 male and 150 female patients from the Leiden University Medical center Neuro Analysis (LUMINA) database. We stratified

patients for sex and treatment location (primary care or secondary care) in order to be able to detect differences between these groups of patients after answering the questions.

The LUMINA database includes over 54,000 adult migraine patients.[9] Enrolment in the LUMINA project started in 2008 via a dedicated website, with the aim to compose a cohort of migraine patients who can be invited to participate in research projects. Migraine patients throughout the Netherlands are made aware of this website via the media, headache patient organisations and via the outpatient clinic of the Leiden University Medical Center (LUMC). Of all the patients in this database, 87% has been diagnosed as migraine patient by a physician, and 70% uses triptans. Migraine diagnoses are established using a validated questionnaire based on the International Classification of Headache Disorders (ICHD-III).[10] Upon entering the cohort, patients have to fill in an extensive questionnaire. In addition to questions necessary to accurately diagnose migraine, the questionnaire also includes items on demographic factors, acute and prophylactic headache medication use, and migraine attack frequency. The LUMINA project has been approved by the Medical Ethics Committee of the LUMC. All participants of the LUMINA study provided written informed consent.

Delphi questionnaires

Patients were sent an invitation by email to fill in three web-based questionnaires during a 6-month period. In Figure 1 we present the questions asked in the consecutive rounds. The exact content of the questionnaires can be found in Appendix 1.

Round 1

First, we asked patients to provide information about their current headache status: number of migraine attacks per month, duration of migraine attacks, number of headache days per month, recurrence, and medication use.

Second, we posed two open-ended questions:

1. What do you find most bothersome about having a migraine attack?
2. If a new medicine was developed against migraine attacks, what would you wish the effect of this medication to be?

Patients were asked to list a minimum of three and a maximum of five answers, and to rate these answers on a 5-point Likert scale (from 1=not important, to 5=very important).

We then grouped the answers according to the presence of strong similarity. During this process, we followed an inductive method, i.e. answers were examined and those considered to be more or less the same were grouped as one item. No fixed number of items was set beforehand, in order to accommodate all new opinions. The answers were grouped by two of the authors (AS and VdG) separately, to ensure independence
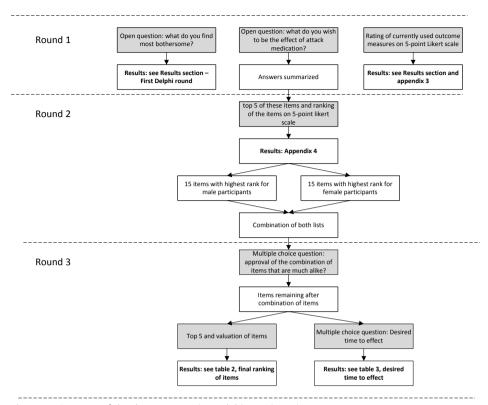
Figure 1. Contents of the three consecutive Delphi questionnaires
Grey boxes: contents of questionnaires
White boxes: actions by researchers

of assessments. Any discrepancies were resolved through a discussion with two other authors (ML and DK), who also checked whether they agreed with the items as formulated by AS and VdG.

Third, we asked patients to rate the relevance of the outcome measures currently used in clinical trials on a 5-point Likert scale (from 1=not important, to 5=very important). We extracted these outcome measures from the most recent guideline for controlled migraine drug trials and from a recently published questionnaire on the evaluation of migraine treatment.[1;11] Patients were asked not to rate a listed outcome measure if they had not experienced it themselves.

The three questions in Round 1 were presented one by one, without the possibility to look back and change answers to the earlier questions. Thus, patients answered the open-ended questions (exploration of patients' opinions) without knowledge of the currently used outcome measures that were mentioned in the last step (existing criteria). In this way we ensured that participants were not informed about the content of the currently used outcome measures when answering the open-ended question.

Round 2

In the Round 2 we presented to the patients the categorized answers to the open-ended question 'What do you find most bothersome about having a migraine attack?' and asked to choose the five most important items and evaluate these on a 5-point Likert scale (from 1=not important, to 5=very important). The respondents were encouraged to comment on the list of items presented to them and to add any items that they felt had been left out.

Round 3

Items from Round 2 were ranked according to the weight-frequency product, that was calculated based on the returned questionnaires, by multiplying the number of times an item was suggested with its mean weight (calculated based on the ranking of items on the Likert scale). In Round 3 we included the items from the top 15 of the male responses and from the top 15 of the female responses.

First, we asked participants if they agreed with the way we combined the items that, in our opinion, reflected the same or very similar content.

Second, we asked patients to select 5 items of the randomly presented list that they considered most crucial in the evaluation of the effect of acute headache medication. We asked patients to value these 5 items by distributing 10 points over these items, such that the item they considered most important was given the highest number of points. Third, we asked participants to indicate how quickly (time to onset) they would want the effect to occur (but only for the symptoms they had experienced themselves).

RESULTS

Participants

Figure 2 presents the flow of participants through the study. Of the 300 patients, the first questionnaire (Round 1) was returned by 169 (56%) patients. Participants and non-participants were compared on the following characteristics available from the LUMINA database: age, educational level, headache subtype, headache frequency, medication use, educational level, anxiety scores, and depression scores (data not shown). Of the 169 participants in Round 1, 62% (n=93) were women (n=93) and 51% were men (n=76). There were no significant differences between participants and non-participants on any of the other characteristics.

Response rates (as percentage of the respondents in the previous round) in the consecutive rounds were high, i.e. 90% in Round 2 and 97% in Round 3.
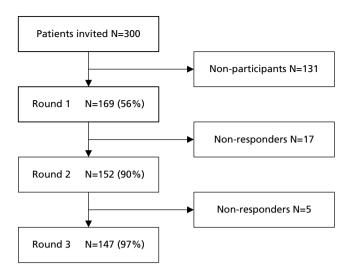
Figure 2. Flowchart of panel member participation

Round 1

Baseline characteristics

The baseline characteristics of participants derived from the first Delphi questionnaire are shown in Table 1.

Table 1. Characteristics of panel members (N=169). Values are means (SD) unless stated otherwise.

Characteristics	
% female	55.0%
Age in years, median (IQR)	47 (40-57)
Years of fulltime education	13.8 (3.6)
HADS total score	11.0 (6.4)
% ≥ 1-4 attacks per month	57.4%
% ≥ 1-4 days per month	74.6%
Number of headache days per month	9.2 (7.8)
Number of migraine headache days per month	7.1 (6.3)
% treatment by general practitioner	48%
% treatment by neurologist	33%
Use of a simple analgesic*, days per month	5.37 (6.4)
Use of ergotamine per month, days per month	0.04 (0.33)
Use of triptan per month, days per month	5.3 (5.4)
Use of medication per month, days per month	6.9 (5.5)
% use of prophylaxis	37%

HADS = Hospital Anxiety and Depression Scale
* Paracetamol, NSAID, or saridon

First Delphi question: Most bothersome aspects of having migraine attacks

The most frequently mentioned bothersome aspects of having a migraine attack were headache pain (62%) and the impact of migraine headaches on daily life (53%). Answers to this question were similar for male and female respondents. An overview of all answers can be found in Appendix 2.

Second Delphi question: What patients wish to be the effect of attack medication

We grouped the answers to the second Delphi question into 36 categories and presented them to the patient panel again in the second round (see Appendix 3).

Evaluation of currently used outcome measures

The ranking of the currently used outcome measures is presented in Appendix 4. Patients considered the following outcome measures to be the most important for them: decrease of headache, time to effect, no relapse within one day, reliability of medication, and how soon they are able to resume normal activities.

Round 2

Second Delphi question: Patients wishes concerning the effect of attack medication

The ranking of the 36 items, according to their frequency weight products, is presented in Appendix 3. The four highest ranked items were the same for male and female respondents.

Although we were investigating the effect that patients wished their attack medication to have, some participants spontaneously mentioned that they it was important that the cause of their migraine was treated (5th and 6th place in ranking order) and that the medication had no negative effects on the long term (6th and 7th place in ranking order). These items focused on migraine-related aspects rather than on the direct effect of migraine on the patient. Accordingly, these two items were included in the second round to give patients the opportunity to indicate how important they rated these particular aspects. However, after the second round, these types of items were excluded, because our final aim was to compile a short list of outcome measures for migraine research. The excluded items were: 'Have no or fewer side-effects', 'Have no negative effects in the long term', 'Treat the cause', 'Work as effectively each time', 'Not be too expensive', and 'Is easy to take in'. Also, excluded was the item 'Work fast' as information on the time to effect (speed of onset) was addressed in a separate question.

Of the candidate items, four pairs resembled each other to a considerable extent and were therefore combined. For example, we combined the answers 'I want the medicine to clear my head' and 'I want the medicine to enable me to think clearly

again' into 'I want the medicine to enable me to think clearly again'. In the third round we explicitly asked participants if they agreed with our decisions concerning the way these items were combined.

Round 3
Combination of items
More than 60% of participants agreed with our combination of the four pairs of similar items.

Second Delphi question: Patients wishes concerning the effect of attack medication
The final results of the Round 3 are presented in Table 2. The items considered most important were: abolish the headache, prevent the attack from carrying on, no relapse within one day, and let the patient function properly again.

The ranking order for the five highest ranked items did not differ between male and female participants (data not shown). Female participants ranked nausea higher compared to male participants (8th and 15th place in ranking order, respectively). Male

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Table 2. Final results of second Delphi question (third round). Items considered most important by the participants (N=147)

Ranking	Outcome measure	N	Mean item weight (SD)	Frequency-weight product
1	take away the headache	121	3.36 (1.52)	407
2	prevent the attack from carrying through	100	2.55 (1.38)	255
3	make sure another attack follows within a few hours or within a day	83	1.90 (0.96)	158
4	let me function properly again	83	1.64 (1.04)	136
5	clear my head	56	1.41 (0.11)	79
6	take away the pressing or thumping feeling	43	1.61 (0.19)	69
7	take away the nausea	49	1.35 (0.13)	66
8	take away the problems with vision (light flashes, hazy vision, double vision)	30	2.17 (0.25)	65
9	take away the sense of illness during a headache attack	41	1.41 (0.16)	58
10	take away the neck pain	35	1.57 (1.18)	55
11	take away the tiredness	44	1.00 (0.11)	44
12	take way the loss of function (problems with speech, tingling or loss of power in arms/legs)	23	1.70 (0.25)	39
13	take away the persistent headache after the headache attack	27	1.19 (0.16)	32

* Weight frequency product: weight multiplied by number of times it is mentioned

participants ranked problems with vision higher compared to female participants (9th and 13th place in ranking order, respectively). These differences are related to a difference in the incidence of these symptoms between male and female participants (i.e. 25.0% of females always experiences nausea, compared to 15.0% of men; 17.5% of females always experience problems with vision compared to 26.9% of men).

The ranking order of the five highest ranked items did not differ between patients who were treated by a neurologist and those not treated by a neurologist (data not shown). Differences lower in the ranking order are also related to a difference in the incidence of symptoms between these two groups.

Time to effect

The results of the question on speed of onset are presented in Table 3. According to the respondents, the headache pain, the pressing or thumping feeling, and the accompanying symptoms should have disappeared within 30 min. They accepted a slightly longer induction time of 1 hour, for being able to function properly and being able to think clearly again, not feeling lethargic and tired, and being cured of their neck ache.

Table 3. Wishes of patients concerning time to effect (third round). Each symptom only rated by patients who reported that they experienced this symptom themselves

Symptoms	Cumulative percentage of patients						
	N	<15 min	<30 min	<1 h	<two hours	<3 hours	<1 day
Take away the headache	147	32.0	72.1	94.6	98.6	100	100
Make sure I can function properly again	144	12.5	43.1	77.8	89.6	94.4	100
Take away the pressing or thumping feeling	137	27.0	59.1	90.5	95.6	98.5	100
Take away the sense of illness	138	8.7	34.8	76.1	87.0	92.8	100
Take away the problems with vision (light flashes, hazy vision, double vision)	105	33.3	55.2	83.8	90.5	97.1	100
Take away the nausea	132	40.9	61.4	92.4	95.5	99.2	100
Make sure I can think clearly again	137	13.1	39.4	78.1	90.5	96.4	100
Take away the neck pain	112	14.3	33.9	72.3	84.8	91.1	100
Take away the loss of function (problems with speech, tingling or loss of power in arms/legs)	94	31.9	50.0	74.5	86.2	93.6	100
Take away the tiredness	143	7.0	23.8	49.7	67.1	79.0	100

DISCUSSION

Main results

This Delphi study shows that the outcome measure 'pain free within 2 hours' on its own does not sufficiently reflect what is important to migraine patients. Patients want their attack medication to relieve the headache within 30 min, rather than the currently used criterion 'pain free within two hours'. They also want the medication to prevent the attack from carrying on, to prevent recurrence, and allow them to function properly within 1 h. This applies to both male and female patients, and to patients treated by a neurologist and not treated by a neurologist.

Strengths and weaknesses

This is the first study in which migraine patients were specifically asked what they consider important with respect to the development of new attack medication for migraine, in a setting where they were not influenced by their fellow patients and/or an interviewer. This allowed them to freely form and express their personal opinions. Also, the Delphi design enabled us to start with an explorative open-ended question in the first round and, subsequently, to ask patients to evaluate the answers that were given and specify the desired 'time to effect' in the second and third rounds. We consider this a major and distinctive strength and of the present study. In addition, the present study is representative for patients from both general practice and secondary/tertiary care.

The study also has some limitations. First, the population might be somewhat higher educated than the migraine population in general, as they had to fill in questionnaires via internet. Second, inherent to the study is that subjective choices had to be made when formulating items and constructing the questionnaires. However, this was carefully performed by i) involving a health psychologist with no background in migraine research as to enable more objective decision-making, ii) categorising the answers to the open-ended questions independently, and iii) requiring consensus from all authors when designing the questionnaires.

Comparison literature

A telephone survey of migraine patients among the general population showed that migraine patients rate the following items as the most important attributes of acute migraine treatment: complete relief of head pain, lack of recurrence and rapid onset of pain relief. In that survey 71% of the patients wanted the pain to be gone in less than 30 min.[12] After existing outcome measure had been presented to our patients, this Delphi study allowed them to suggest medication effects that they considered to be important; this yielded two new items, i.e. 'Prevention of worsening of the attack' and 'The ability to function properly again within 1 hour'.

It is reported that most migraine patients (54%) do not notice any benefit in the first hour after taking headache medication.[13] Remarkably, although the wish for a faster effect of attack medication was already expressed by patients in a study published in 1999[12], the outcome measures used in the evaluation of medication have not yet been altered.

Conclusions

The currently used outcome measures in migraine research do not sufficiently reflect the expectations of migraine patients. The present study shows that patients wish their headache to be abolished within 30 min. It seems that, until now, research on migraine medication has been guided by what was considered possible and not by the actual wishes/expectations of migraine patients. The results of the present study clearly indicate that treatment should focus on: being pain free rapidly, preventing the migraine from becoming worse, preventing the recurrence of migraine, restoring proper function and permitting patients to think clearly again within an hour. Future research should aim to develop an outcome measure that combines all these aspects and thereby enable measurement of what migraine patients find most important.

REFERENCES

1.   Tfelt-Hansen P, Pascual J, Ramadan N, Dahlof C, D'Amico D, Diener HC et al. Guidelines for controlled trials of drugs in migraine: third edition. A guide for investigators. Cephalalgia 2012;32:6-38.

2.   Lipton RB, Hamelsky SW, Dayno JM. What do patients with migraine want from acute migraine treatment? Headache 2002;42:S3-S9.

3.   Hamelsky SW, Lipton RB, Stewart WF. An assessment of the burden of migraine using the willingness to pay model. Cephalalgia 2005;25:87-100.

4.   Selby JV, Beal AC, Frank L. The Patient-Centered Outcomes Research Institute (PCORI) national priorities for research and initial research agenda. JAMA 2012;307:1583-1584.

5.   Jones J, Hunter D. Qualitative research: consensus methods for medical and health services research. BMJ 1995;311:376.

6.   Hasson F, Keeney S, McKenna H. Research guidelines for the Delphi survey technique. J Adv Nurs 2000;32:1008-1015.

7.   Kirwan JR, Minnock P, Adebajo A, Bresnihan B, Choy E, de WM et al. Patient perspective: fatigue as a recommended patient centered outcome measure in rheumatoid arthritis. J Rheumatol 2007;34:1174-1177.

8.   Van der Heijden GJ, Leffers P, Bouter LM. Shoulder disability questionnaire design and responsiveness of a functional status measure. J Clin Epidemiol 2000;53:29-38.

9.   Van Oosterhout WP, Weller CM, Stam AH, Bakels F, Stijnen T, Ferrari MD et al. Validation of the web-based LUMINA questionnaire for recruiting large cohorts of migraineurs. Cephalalgia 2011;31:1359-1367.

10.   The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 2013;33:629-808.

11.   Coon CD, Fehnel SE, Davis KH, Runken MC, Beach ME, Cady RK. The development of a survey to measure completeness of response to migraine therapy. Headache 2012;52:550-572.

12.   Lipton RB, Steward WF. Acute migraine therapy: do doctors understand what patients with migraine want from therapy? Headache 1999;39:S20-S26.

13.   Bigal M, Rapoport A, Aurora S, Sheftell F, Tepper S, Dahlof C. Satisfaction with current migraine therapy: experience from 3 centers in US and Sweden. Headache 2007;47:475-479.

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APPENDIX 1. QUESTIONNAIRES

Questionnaire round 1

1. How many severe headache attacks have you experienced in the past 12 months?
- ☐ 1 - 2
- ☐ 3 - 6 (i.e. on average one attack per 2 - 4 months)
- ☐ 7 - 12 (i.e. on average one attack per 1 - 2 months)
- ☐ 13 - 54 (i.e. on average one to four attacks per month)
- ☐ more than 54 (i.e. multiple attacks per week)
- ☐ multiple attacks per day
- ☐ I had a headache almost continuously without increased paroxysm

2. On how many days in the past 12 months did you experience severe headaches?
- ☐ 1 - 2
- ☐ 3 - 6 (i.e. on average one day per 2 - 4 months)
- ☐ 7 - 12 (i.e. on average one day per 1 - 2 months)
- ☐ 13 - 54 (i.e. on average one to four days per month)
- ☐ more than 54 (i.e. multiple days per week)
- ☐ almost every day

3. On how many days per month did you experience headaches in the past 3 months?
 [………] days per month

4. On how many of those days did you experience severe paroxysmal headache?
        [………] days per month

5. Preventive medication (to prevent occurrence of headache)
The following question is about preventive medication that was prescribed to you by a medical doctor to prevent headache complaints (e.g. propanolol (Inderal), metoprolol (Selokeen, Lopresor), natriumvalproate (Depakine), topiramate (Topamax), flunarizine (Sibelium), pizotifeen (Sandomigran)).

5A. Are you taking daily prophylactic medication prescribed to you by a medical doctor to prevent your complaints?
- ☐ no   *[➔   go directly to question 6]*
- ☐ yes

You only need to fill in this question if 5A=yes

5B. Please write down the name of your daily preventive medication.
[………………………………]

6. Medication to be taken during an attack
The following questions are supplementary questions about your medication use. We ask about the number of days that you use certain medication against headache complaints. We ask you to take the mean use of the last three months. If you take less than 1 dose per month, we ask you to fill in a 0. Also, if you take a medication (almost) never, we ask you to fill in a 0.

6A. On how many days in the past 3 months did you use simple analgesics, such as paracetamol, aspirin, naproxen, diclofenac, ibuprofen, saridon etc.?
[………] days per month

6B. On how many days in the past 3 months did you use ergotamines, such as cafergot, ergocaffeine?
[………] days per month

6C. On how many days in the past 3 months did you use triptans, such assumatriptan (Imigran), eletriptan (Relpax), rizatriptan (Maxalt), almotriptan (Almirall), zolmitriptan (Zomig), frovotriptan (Fromirex) of naratriptan (Naramig))?
 [………] days per month

6D. Possibly there are days on which you take several kinds of medication. On how many days per month do you take any kind of medication against your headache?
[………] days per month

7. Treatment
7A. Are you currently being treated by a general practitioner for your migraine?
☐ no
☐ yes
7B. Are you currently being treated by a neurologist for your migraine?
☐ no
☐ yes

People perceive different things as bothersome when having a migraine attack. We would like to know what things you find bothersome about having a migraine attack.

8. What do you find most bothersome about having a migraine attack? Please mention at least 3 and maximum 5 things that you find bothersome about having a migraine attack. Please indicate how bothersome you find these things on a 5-point scale.

Things that are bothersome about having a migraine attack	How bothersome? 1 = not at all bothersome 5 = very bothersome	Additional remarks (If you wish, you can add an additional remark)
	1 2 3 4 5	
	1 2 3 4 5	
	1 2 3 4 5	
	1 2 3 4 5	
	1 2 3 4 5	

People have different expectations from migraine medication. We would like to know which complaints you want to be treated.

9. If a new medicine was to be developed against migraine attacks, what would you wish the effect to be? Please mention at least 3 and maximum 5 things that you find important as a result of attack medication for migraine. Please indicate how important you consider these things.

What do you expect from migraine medication?	How important? 1 = not important 5 = very important	Additional remarks (If you wish, you can add an additional remark)
	1 2 3 4 5	
	1 2 3 4 5	
	1 2 3 4 5	
	1 2 3 4 5	
	1 2 3 4 5	

10. You have indicated what you considered important in the treatment of your migraine attacks. Below is an overview of aspects in which research is being done about new medication. We would like to know how you consider these. Do you consider it to be important, less important or not important? Could you indicate, per subject, how important you consider it to be? If the subject is not applicable to you (e.g. because you have never suffered from it), you may indicate 'not applicable to me'. Finally, there is some space to add additional remarks that you think are missing from the list.

Subject	How important? 1 = not very important 5 = very important	Not applicable to me	Additional remarks (If you wish, you can add an additional remark)
Decrease of the headache	1 2 3 4 5		
Decrease of nausea	1 2 3 4 5		
Decrease of light sensitivity	1 2 3 4 5		
Decrease of noise sensitivity	1 2 3 4 5		
Decrease in neck/shoulder pain	1 2 3 4 5		
Decrease in irritability	1 2 3 4 5		
Rate at which you can think clearly again after taking medication	1 2 3 4 5		
Is one tablet/suppository/ injection/spray sufficient?	1 2 3 4 5		
How quickly you can resume your activities	1 2 3 4 5		
How quickly you feel completely recovered	1 2 3 4 5		
The length of time for the medication to take effect	1 2 3 4 5		
Do complaints return within one day?	1 2 3 4 5		
Does the medication as effectively with each attack?	1 2 3 4 5		
Do you suffer from side-effects?	1 2 3 4 5		

11. Additional remarks about the questionnaire

Please write down below any comments about the questionnaire.

Questionnaire round 2

In the previous questionnaire we asked you to name aspects that were most important to you in the treatment of a migraine attack. Below, all the answers are presented.

Part A
Could you indicate per answer how important this aspect is to you on a scale of 1 (not important) to 5 (very important)?
The medication must:

1. take away the irritability or moodiness *prior to a headache attack*
2. take away the other preceding phenomena (such as (binge)eating, yawning)
3. prevent the attack from carrying on
4. take away the problems with vision *prior to a headache attack* (light flashes, hazy vision, double vision)
5. take way the loss of function (problems with speech, tingling or loss of power in arms/legs)
6. take away the headache
7. take away the pressing or thumping feeling
8. take away the nausea
9. prevent me from having to throw up
10. take away the neck pain
11. take away the shoulder pain
12. take away the problems with vision *during the headache attack* (light flashes, hazy vision, double vision)
13. clear my head
14. make sure I can think clearly again
15. take away the sensitivity to outside stimulants (light, noise, or smells)
16. make sure my sense of taste is normal again
17. take away the irritability or moodiness *during a headache attack*
18. take away the sense of illness *during a headache attack*
19. take away the tiredness *during a headache attack*
20. let me function properly again
21. that I no longer have sensitive skin
22. take away the bowel complaints
23. take away the dizziness *during a headache attack*
24. let me be able to relax
25. let me be able to sleep
26. take away the persistent headache *after the headache attack*
27. take away the tiredness *after a headache attack*
28. take away the sense of illness *after a headache attack*

29. make sure another attack does not follow within a few hours or within one day
30. work fast
31. have no or fewer side-effects
32. have no negative effects in the long term
33. treat the cause
34. work as well each time
35. not be too expensive
36. is easy to swallow/take in

Part B

Of the above aspects, which 5 do you consider the most important and must definitely be included in the development of new medication against migraine attacks?
Could you rank what you consider to be the most important aspect as number 1, the next most important as number 2, etc.

☐ must take away the irritability or moodiness *prior to a headache attack*
☐ take away the other preceding phenomena (such as (binge)eating, yawning)
☐ prevent the attack from carrying on
☐ take away the problems with vision *prior to a headache attack* (light flashes, hazy vision, double vision)
☐ take away the loss of function (problems with speech, tingling or loss of power in arms/legs)
☐ take away the headache
☐ take away the pressing or thumping feeling
☐ take away the nausea
☐ prevent me from having to throw up
☐ take away the neck pain
☐ take away the shoulder pain
☐ take away the problems with vision *during the headache attack* (light flashes, hazy vision, double vision)
☐ clear my head
☐ make sure I can think clearly again
☐ take away the sensitivity to outside stimulants (light, noise, or smells)
☐ make sure my sense of taste is normal again
☐ take away the irritability or moodiness *during a headache attack*
☐ take away the sense of illness *during a headache attack*
☐ take away the tiredness *during a headache attack*
☐ let me function properly again
☐ that I no longer have sensitive skin
☐ take away the bowel complaints

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- ☐ take away the dizziness *during a headache attack*
- ☐ let me be able to relax
- ☐ let me be able to sleep
- ☐ take away the persistent headache *after the headache attack*
- ☐ take away the tiredness *after a headache attack*
- ☐ take away the sense of illness *after a headache attack*
- ☐ make sure another attack does not follow within a few hours or within one day
- ☐ work fast
- ☐ have no or fewer side-effects
- ☐ have no negative effects on the long term
- ☐ treat the cause
- ☐ work as effectively each time
- ☐ not be too expensive
- ☐ is easy to swallow/take in

Could you indicate below which aspects you still miss and that, in your opinion, should definitely be included in the review of the efficacy of the new medication?

Questionnaire round 3

<u>Part A</u>

As a result of the answers to the previous questions we have combined some of the questions. We would like to know whether, in your opinion, you feel that these questions can be combined. It might be that you would give a different answer to the individual questions and that, therefore, they individual questions should not be combined.

Below, each time, we present two questions from the previous round with our proposal as how to they can be combined. We would like to know whether you agree with the way we have combined them.

Answering options:
- Agree: these two items can be combined
- Disagree: these two items should remain separated, because they ask about different aspects

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1.
Questions from the previous round:
- take away the problems with vision *prior to the headache attack* (light flashes, hazy vision, double vision)
- take away the problems with vision *during the headache attack* (light flashes, hazy vision, double vision)

Combined to:
- take away the problems with vision prior to or during the headache attack (light flashes, hazy vision, double vision).

2.
Questions from the previous round:
- clear my head again
- make sure I can concentrate again

Combined to:
- make sure I can think clearly again

3.

Questions from the previous round:

- take away the nausea
- make sure I do not have to vomit

Combined to:

- take away the nausea

4.

Questions from the previous round:

- take away the tiredness *after the headache attack*
- take away the tiredness *during the headache attack*

Combined to:

- take away the tiredness during or after the headache attack

Part B

Below, we list the items from the previous round that were indicated to be the most important aspects regarding the effect which new migraine medication should have. From the list, please choose 5 aspects that are the most important to you.

To have an idea of how important you consider the various aspects, we ask you to distribute 10 points over the 5 aspects you have chosen, based on their level of importance. Thus, an important item will be given more points than a less important item.

Examples:

1. You experience aspect 1 as very important, whereas you do not find the other aspects to be important at all. In this case, you fill in:

a. Effect 1   10 points
b. Effect 6   0 points
c. Effect 2   0 points
d. Effect 3   0 points
e. Effect 4   0 points

2. You experience aspect 1 and aspect 6 to be the most important. In addition, you consider aspect 2 to be fairly as important and aspects 3 and 4 to be only slightly important. In this case, you fill in:

a. Effect 1   3 points
b. Effect 6   3 points
c. Effect 2   2 points

d.   Effect 3   1 point
e.   Effect 4   1 point

The medication must …
1.   take away the headache
2.   prevent the attack from carrying on
3.   make sure another attack does not follow within a few hours or within one day
4.   let me function properly again
5.   take away the pressing or thumping feeling
6.   take away the sense of illness *during a headache attack*
7.   take away the problems with vision (light flashes, hazy vision, double vision)
8.   take away the nausea
9.   make sure I can think clearly again
10. take away the persistent headache *after the headache attack*
11. take away the neck pain
12. take way the loss of function (problems with speech, tingling or loss of power in arms/legs)
13. take away the tiredness

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Part C
For some of the aspects, we would like to know whether you still suffer, or have suffered from these items with your migraine attacks.

Answering options:
i.   I never have this
ii.   I sometimes have this
iii. I often have this
iv.   I always have this

1.   headache
2.   pressing or thumping feeling
3.   sense of illness
4.   problems with vision (light flashes, hazy vision, double vision)
5.   nausea
6.   not being able to think clearly
7.   persistent headache *after the headache attack*
8.   neck pain
9.   loss of function (problems with speech, tingling or loss of power in arms/legs)
10. tiredness

Part D

In the previous list of questions many people indicated that the speed at which the medication acts is important. We would like to know from you, how fast you would like the medication to act on particular symptoms.

How fast should the following effects of the medication take place?

Answering options:
a. within fifteen minutes
b. within thirty minutes
c. within 1 h
d. within two hours
e. within three hours
f. within one day
g. I never suffer from this symptom

1. take away the headache
2. make sure I can function properly again
3. take away the pressing or thumping feeling
4. take away the sense of illness *during a headache attack*
5. take away the problems with vision (light flashes, hazy vision, double vision)
6. take away the nausea
7. make sure I can think clearly again
8. take away the neck pain
9. take away the loss of function (problems with speech, tingling or loss of power in arms/legs)
10. take away the tiredness

APPENDIX 2. CATEGORIZED ANSWERS TO THE FIRST DELPHI QUESTION (ROUND 1): 'What do you consider to be the most bothersome about having migraine attacks?'

	Men (%) (n=76)	Women (%) (n=93)	P-value*	Total
Headache	42 (55.3)	62 (66.7)	0.13	104
Not being able to function normally and the impact on social life/work/family	44 (57.9)	55 (59.1)	0.87	98
Nausea/vomiting, less appetite during attack	30 (39.5)	45 (48.4)	0.25	75
Hypersensitivity to light, sound, smell	12 (15.8)	30 (32.3)	0.01	42
Tiredness, yawning	13 (17.1)	22 (23.7)	0.30	35
Problems with concentration, sense of absence	17 (22.4)	17 (18.3)	0.51	34
Visual (aura) phenomena	14 (18.4)	12 (12.9)	0.32	26
Psychological consequences (anxiety, gloom)	13 (17.1)	13 (14.0)	0.58	26
Irritability/moodiness	8 (10.5)	13 (14.0)	0.50	21
Recovery period after the attack (tiredness, concentration problems, sense of illness)	6 (7.9)	10 (10.8)	0.53	16
The need to take medication	4 (5.30	10 (10.8)	0.20	14
General sense of illness	4 (5.3)	9 (9.7)	0.28	13
Neurological loss of function (not being able to speak properly, not being able to come to words, loss of function in the face/limbs)	4 (5.3)	8 (8.6)	0.40	12
Unpredictability of attacks	5 (6.6)	4 (4.3)	0.51	10
That it lasts several days	4 (5.3)	6 (6.5)	0.75	10
Aura (not specified)	7 (9.2)	2 (2.2)	0.42	9
Sleeping problems (sleeping badly, sleeping a lot)	6 (7.9)	3 (3.2)	0.18	9
Misunderstanding from the surroundings	4 (5.30	2 (2.2)	0.28	6
Neck pain	2 (2.6)	6 (5.6)	0.25	8
Dizziness	4 (5.3)	1 (1.1)	0.11	5
Phenomena prior to attack#	0 (0.0)	3 (3.2)	0.11	3
Changed sense of taste	0 (0.0)	2 (2.2)	0.20	2
Pain to touch (face, ears)	0 (0.0)	2 (2.2)	0.20	2
Total	243	335		578

* Chi square test

Not otherwise specified, binge eating, disorientation

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APPENDIX 3. RANKING OF THE 36 ITEMS IN THE SECOND DELPHI ROUND FOR FEMALE AND MALE RESPONDENTS (ROUND 2)

	Female respondents	N	Mean item weight (SD)	Male respondents	N	Mean item weight (SD)
1	take away the headache	63	4.98 (0.16)	take away the headache	50	4.92 (0.27)
2	prevent the attack from carrying on	45	4.96 (0.21)	prevent the attack from carrying on	31	5.00 (0.00)
3	make sure another attack does not follow within a few hours or within one day	38	4.97 (0.16)	let me function properly again	26	4.54 (0.76)
4	let me function properly again	29	4.86 (0.44)	make sure another attack does not follow within a few hours or within one day	22	4.95 (0.21)
5	take away the pressing or thumping feeling	25	4.92 (0.28)	have no negative effects on the long term	20	4.95 (0.22)
6	have no negative effects on the long term	20	5.00 (0.00)	treat the cause	20	4.45 (1.05)
7	treat the cause	20	4.40 (0.99)	work fast	17	4.41 (1.06)
8	work fast	17	4.82 (0.53)	take away the pressing or thumping feeling	15	4.87 (0.35)
9	take away the nausea	15	5.00 (0.00)	take away the sense of illness during a headache attack	13	4.69 (0.48)
10	work as effectively each time	12	4.75 (0.45)	make sure I can think clearly again	11	4.73 (0.65)
11	take away the problems with vision prior to a headache attack (light flashes, hazy vision, double vision)	12	4.67 (0.65)	take away the problems with vision prior to a headache attack (light flashes, hazy vision, double vision)	11	4.64 (0.81)
12	have no or fewer side-effects	12	4.58 (1.16)	clear my head	9	4.78 (0.44)
13	take away the persistent headache after the headache attack	12	4.50 (0.52)	prevent me from having to throw up	9	4.56 (1.01)
14	take way the loss of function (problems with speech, tingling or loss of power in arms/legs)	11	4.82 (0.40)	work as effectively each time	8	5.00 (0.00)
15	take away the tiredness after a headache attack	11	4.55 (0.69)	take away the problems with vision during the headache attack (light flashes, hazy vision, double vision)	8	4.63 (0.52)
16	take away the neck pain	10	4.90 (0.32)	take away the persistent headache after the headache attack	7	4.86 (0.38)
17	take away the sense of illness during a headache attack	11	4.45 (0.69)	take away the tiredness during a headache attack	7	4.71 (0.49)

#	Item	n	Mean (SD)	Item	n	Mean (SD)
18	prevent me from having to throw up	10	4.70 (0.67)	let me be able to sleep	7	4.57 (0.79)
19	make sure I can think clearly again	9	4.56 (0.53)	take away the neck pain	7	4.43 (0.79)
20	take away the sensitivity to outside stimulants (light, noise, or smells)	7	4.29 (0.76)	take away the nausea	7	4.29 (0.79)
21	take away the problems with vision during the headache attack (light flashes, hazy vision, double vision)	6	4.83 (0.41)	let me be able to relax	5	4.80 (0.45)
22	let me be able to sleep	6	4.67 (0.52)	take way the loss of function (problems with speech, tingling or loss of power in arms/legs)	5	4.60 (0.89)
23	be easy to swallow/take in	5	5.00 (0.00)	take away the tiredness after a headache attack	5	4.60 (0.89)
24	take away the tiredness during a headache attack	4	4.50 (0.58)	have no or fewer side-effects	5	4.60 (0.55)
25	clear my head	3	4.67 (0.58)	take away the sensitivity to outside stimulants (light, noise, or smells)	4	4.75 (0.50)
26	take away the sense of illness after a headache attack	3	4.67 (0.58)	take away the shoulder pain	3	4.67 (0.58)
27	take away the other preceding phenomena (such as (binge) eating, yawning)	1	5.00 (-)	take away the bowel complaints	3	4.67 (0.58)
28	take away the irritability or moodiness during a headache attack	1	5.00 (-)	take away the irritability or moodiness prior to a headache attack	3	4.33 (1.15)
29	take away the bowel complaints	1	5.00 (-)	be easy to swallow/take in	3	3.67 (2.31)
30	take away the dizziness during a headache attack	1	5.00 (-)	take away the dizziness during a headache attack	2	4.50 (0.71)
31	let me be able to relax	1	5.00 (-)	take away the other preceding phenomena (such as (binge)eating, yawning)	2	3.00 (2.83)
32	make sure my sense of taste is normal again	1	4.00 (-)	not be too expensive	1	4.00 (-)
33	take away the irritability or moodiness prior to a headache attack	1	1.00 (-)	take away the sense of illness after a headache attack	1	3.00 (-)
34	take away the shoulder pain	0	–	make sure my sense of taste is normal again	0	–
35	make sure I no longer have a sensitive skin	0	–	take away the irritability or moodiness during a headache attack	0	–
36	not be too expensive	0	–	make sure I no longer have a sensitive skin	0	–

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APPENDIX 4. EVALUATION OF CURRENT OUTCOME MEASURES RANKED IN ORDER OF IMPORTANCE (FIRST ROUND)

Outcome measure	n[*]	% of total	Mean (SD)
Decrease of headache	168	99.4	4.9 (0.4)
Time to effect	169	100	4.6 (0.7)
Relapse within one day	165	98.0	4.5 (0.8)
Reliability of medication	168	99.4	4.5 (0.7)
How soon able to resume normal activities	167	98.8	4.5 (0.8)
How soon feeling completely well	169	100	4.4 (0.9)
How soon being able to think clearly	163	96.4	4.3 (1.0)
Decrease of nausea	139	82.2	4.1 (1.0)
Adverse events	162	95.9	4.1 (1.0)
If more than 1 dose needed	168	99.4	3.9 (1.3)
Decrease of photophobia	141	83.4	3.7 (1.4)
Decrease of shoulder and/or neck pain	133	78.7	3.7 (1.3)
Decrease of irritability	149	88.2	3.7 (1.2)
Decrease of phonophobia	147	87.0	3.6 (1.2)

[*] Number of patients who experience this symptom during their migraine attacks.