

Editor's Summary

Placebo and Medication Effects in Episodic Migraine

Placebo and medication effects are intimately related in clinical practice and drug development. In new work, Kam-Hansen *et al.* investigated how information—ranging from "negative" to "neutral" to "positive"—provided to patients, who received either active drug or placebo, modified their headache pain as measured by patient-reported pain scores. In a randomized order over six consecutive attacks, 66 patients with episodic migraine received either placebo or Maxalt (10-mg rizatriptan) under three information conditions (told placebo, told Maxalt or placebo, told Maxalt). Each participant also reported on an initial no-treatment attack, yielding a total of 459 documented migraine attacks. Maxalt was superior to placebo for pain relief. Increasing information from negative to neutral to positive progressively enhanced the effects of both placebo and Maxalt. The efficacy of open-label placebo was superior to that of no treatment. Relative to no treatment, the placebo, under each information condition, accounted for more than 50% of the drug effect. The benefits of placebo persisted even when the placebo was honestly described. Whether treatment involves medication or placebo, the information provided to patients and the ritual of pill taking are important components of medical care.

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MIGRAINE

Altered Placebo and Drug Labeling Changes the Outcome of Episodic Migraine Attacks

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Information provided to patients is thought to influence placebo and drug effects. In a prospective, within-subjects, repeated-measures study of 66 subjects with episodic migraine, we investigated how variations in medication labeling modified placebo and drug effects. An initial attack with no treatment served as a control. In six subsequent migraine attacks, each participant received either placebo or Maxalt (10-mg rizatriptan) administered under three information conditions ranging from negative to neutral to positive (told placebo, told Maxalt or placebo, told Maxalt) ($N = 459$ documented attacks). Treatment order was randomized. Maxalt was superior to placebo for pain relief. When participants were given placebo labeled as (i) placebo, (ii) Maxalt or placebo, and (iii) Maxalt, the placebo effect increased progressively. Maxalt had a similar progressive boost when labeled with these three labels. The efficacies of Maxalt labeled as placebo and placebo labeled as Maxalt were similar. The efficacy of open-label placebo was superior to that of no treatment. Relative to no treatment, the placebo, under each information condition, accounted for more than 50% of the drug effect. Increasing “positive” information incrementally boosted the efficacy of both placebo and medication during migraine attacks. The benefits of placebo persisted even if placebo was honestly described. Whether treatment involves medication or placebo, the information provided to patients and the ritual of pill taking are important components of care.

INTRODUCTION

It is generally thought that placebo and medication efficacies are influenced by contextual factors such as the expectations embedded in the information clinicians provide (1). Much of the evidence for such beliefs is based on “balanced placebo design” experiments concerning mostly addictive or stimulant substances or their placebo controls that disentangle and reassemble placebo and medication effects by providing subjects with various statements, including true and false information. These between-subjects studies have shown that information can significantly modulate the impact of such substances (2–6).

To ascertain whether these findings apply in a clinical condition, we used a randomized 2×3 within-subjects expanded “balanced placebo design” to test the hypothesis that, in acute migraine, clinical outcomes with both placebo and medication treatment would increase progressively as information varied from negative (0% chance of receiving active medication) to uncertain (50% chance of medication) to positive (100% chance) (ClinicalTrials.gov identifier: NCT00719134). A seventh session provided a no-treatment baseline. As secondary questions, we planned to examine whether medication with negative information was different from placebo with positive information and whether open-label placebo was superior to no-treatment control. In an exploratory fashion, we also planned to examine whether the difference between medication

and placebo changed under varying information conditions. We used migraine headache as a model because it is a naturally recurring neurological disorder of unilateral throbbing headache associated with variable incidence of aura, nausea, photophobia, allodynia, fatigue, and irritability (7). The recurring nature of migraine allowed us to compare for each subject the efficacies of treatment and placebo over consecutive attacks using varying conditions of information.

RESULTS

Study design

Participants were required to document one untreated attack at the beginning of the study and six subsequent attacks randomly assigned for treatment with a pill of rizatriptan (10-mg Maxalt) or placebo, each labeled once as “Maxalt,” once as “placebo,” and once as “Maxalt or placebo” (Fig. 1 and Table 1). They were asked to record one pain score 30 min after the onset of headache (baseline), take the study pill at the same baseline time (but not in an untreated attack), and record a second pain score 2.5 hours after the onset of headache. Rescue medications were provided for each attack to be used as needed 2.5 hours after the onset of headache. Baseline pain scores were reported in 459 attacks, whereas the 2.5-hour pain scores were reported in 435 attacks. Using additional information available in the diaries, we were able to impute 18 of the missing pain scores at 2.5 hours, resulting in 453 analyzable attacks (Table 2 and table S1). Generalized linear mixed models were used to analyze the data as described in detail in Materials and Methods and Supplementary Methods.

Participant enrollment and characteristics

Of 98 persons prescreened for eligibility between December 2008 and March 2010, 19 were excluded for reasons listed in table S2,

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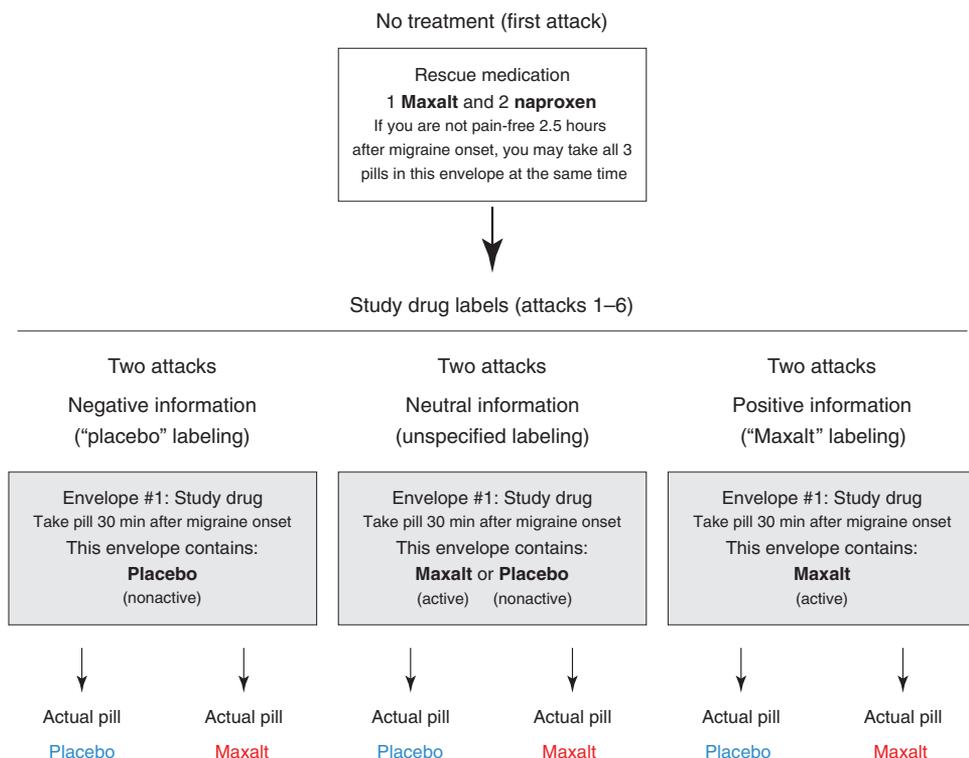


Fig. 1. Labeling of the "study drug" and optional "rescue medications" envelopes. The study drug envelope was labeled "placebo" (two attacks), "Maxalt or placebo" (two attacks), or "Maxalt" (two attacks) to provide negative, neutral, or positive information, respectively. Subjects were instructed to open the envelope and take the pill 30 min after onset of headache. They were asked to refrain from taking rescue medications during the first 2.5 hours of each attack, including attack 1 (no treatment).

Table 1. Study design combining three types of labeling and two types of treatment.

Labeling of treatment pill	Accuracy of treatment labeling	
	Given placebo pill	Given Maxalt pill
Placebo (negative information)	Correct	Incorrect
Maxalt or placebo (neutral information)	Correct	Correct
Maxalt (positive information)	Incorrect	Correct

and 3 declined to participate. The remaining 76 persons signed the consent form, but 10 of them dropped out of the study for various reasons (Fig. 2). The demographic characteristics of the 66 participants and the 10 dropouts were very similar (table S3). Participants had experienced a median of 4 episodic migraine attacks per month [interquartile range (IQR), 2 to 8], cumulatively lasting a median of 4 (IQR, 3 to 8) migraine days per month (table S4); 25% of them used migraine prophylactic drugs. Of the 66 participants, 51 provided complete data on all seven attacks, and 15 submitted incomplete data on one to three attacks and complete data on the remaining attacks (Fig. 2). None of the subjects reported any unexpected adverse event other than the typical side effects listed in the drug information.

Primary endpoint

The primary outcome measure was the change in headache between the baseline pain score recorded 30 min after the onset of headache and the pain score recorded 2 hours later. Baseline average pain scores, measured on a numerical scale ranging from 0 (no pain) to 10 (maximal pain), at time of treatment were comparable among the six treated migraine attacks ($P = 0.75$) (Table 2). Compared with baseline, the typical pain score in the untreated attack was higher after 2 hours ($P = 0.037$); in the treated attacks, the typical pain score was lower after 2 hours ($P \leq 0.015$). Table 2 provides the means and SDs of pain scores at 30 min and 2.5 hours by experimental condition.

Both labeling of the pill ("placebo," "Maxalt or placebo," "Maxalt") ($P = 0.010$) and treatment (Maxalt, placebo) ($P < 0.001$) had statistically significant effects on the difference in pain scores between baseline and 2 hours after treatment, but the two factors had no significant interaction ($P = 0.37$). The lack of a significant interaction allowed the labeling effect to be summarized across treatments and the drug effect to be summarized across labels. The typical decrease in pain score was 26.1% [confidence interval (CI), 18.2 to 33.2%] with "placebo" labeling, 40.1% (CI, 32.1 to 47.0%) with "Maxalt or placebo" labeling, and 39.5% (CI, 31.7 to 46.5%) with "Maxalt" labeling. The typical decrease in pain score was 47.6% (CI, 41.5 to 53.0%) for Maxalt treatment versus 20.7% (CI, 14.3 to 26.7%) for placebo treatment.

In secondary analyses, we found that even when placebo treatment was labeled accurately and openly described as placebo, pain scores typically decreased by 14.5% (CI, 2.9 to 24.6%). This contrasted significantly with the untreated attack ($P = 0.001$), during which pain scores typically rose by 15.4% (CI, 0.9 to 31.9%). The efficacy of 10-mg Maxalt that was mislabeled as placebo was not significantly different from the efficacy of placebo treatment that was mislabeled as Maxalt (36.1 versus 24.6%, $P = 0.127$, Fig. 3).

Notably, the placebo effect in this experiment was quite robust and more than half as large as the effect of Maxalt treatment. Relative to the no-treatment condition (15.4% increase in pain), the effect of placebo under "placebo" labeling (14.5 + 15.4%) was 60.0% as large as the corresponding effect of Maxalt treatment (36.1 + 15.4%). Similarly, the placebo effect was 59.8% as large as the Maxalt effect under "Maxalt" labeling and 55.3% as large under "Maxalt or placebo" labeling.

Secondary endpoint

A secondary measure of attack outcome was based on categorical classification of the pain freedom (pain score = 0) 2.5 hours after onset of headache. The proportion of participants who were pain-free varied significantly among the six treated attacks ($P < 0.001$). Treatment had statistically significant effects ($P < 0.001$), but labeling did not

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Table 2. Mean pain scores in the seven study attacks.

Pill	Label	Number of attacks (n) and mean (SD) pain scores					
		Available values		Available values		Available and imputed values	
		n	0.5 hour	n	2.5 hours	n	2.5 hours
None	No treatment	66	4.6 (1.8)	63	5.3 (2.4)	66	5.4 (2.4)
Placebo	Placebo	65	5.9 (2.1)	57	4.8 (3.0)	63	5.0 (3.0)
	Maxalt or placebo	66	5.7 (2.0)	63	4.2 (2.6)	66	4.3 (2.7)
	Maxalt	66	5.7 (2.0)	62	4.2 (2.9)	65	4.2 (2.9)
Maxalt	Placebo	65	5.6 (2.1)	63	3.3 (2.9)	65	3.4 (3.0)
	Maxalt or placebo	65	5.5 (2.0)	64	2.4 (2.8)	65	2.4 (2.8)
	Maxalt	66	5.6 (1.9)	63	2.5 (3.0)	63	2.5 (3.0)
Total number of attacks		459		435		453	

($P = 0.053$); treatment and labeling had no significant interaction ($P = 0.48$) (Fig. 4). The typical percentage of participants who were free from pain was 25.5% (CI, 17.2 to 36.0%) for all Maxalt treatments versus 6.6% (CI, 3.4 to 12.2%) for all placebo treatments. The typical percentage of participants who were pain-free was 16.6% (CI, 9.6 to 27.3%) for “Maxalt” labeling versus 9.2% (CI, 4.7 to 17.2%) for “placebo” labeling ($P = 0.082$). The typical percentage of participants who were pain-free for “Maxalt or placebo” labeling was 15.5% (CI, 8.8 to 25.9%).

Unlike the primary endpoint, the proportion of participants who were pain-free during the no-treatment condition (0.7%) was not statistically different from when participants took open-label placebo (5.7%). As with the primary endpoint, the proportion of participants pain-free after treatment was not statistically different between Maxalt treatment mislabeled as placebo (14.6%) and placebo treatment mislabeled as Maxalt (7.7%). The resulting therapeutic gain (that is, drug-placebo difference) was 8.8 percentage points under “placebo” labeling [odds ratio (OR), 2.80], 26.6 percentage points under “Maxalt or placebo” labeling (OR, 7.19), and 24.6 percentage points under “Maxalt” labeling (OR, 5.70).

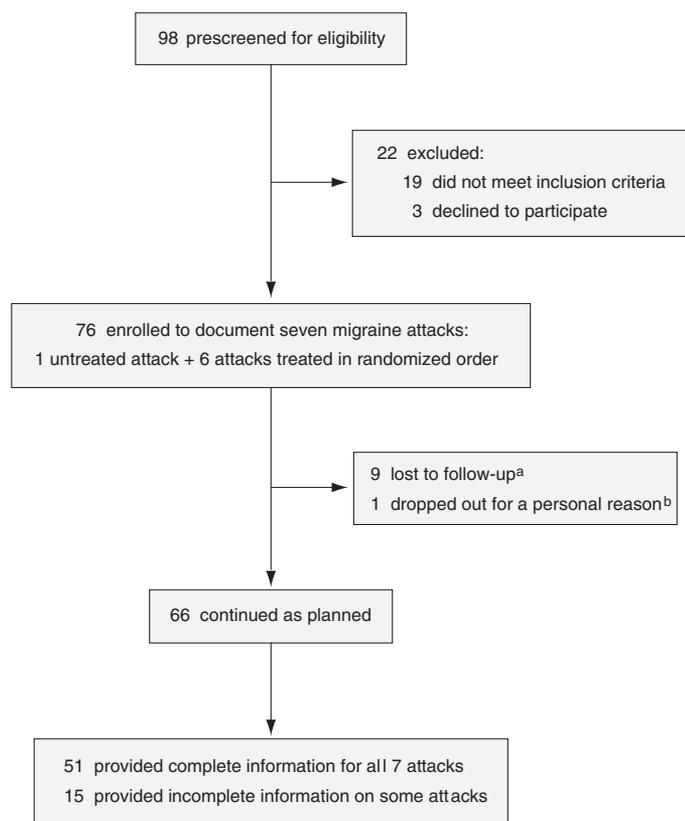


Fig. 2. Flow diagram of disposition of patients, after the Consolidated Standards for Reporting of Trials (CONSORT). The steps lead from pre-screening to collection of the data used in the analysis. The diagram shows the extent of exclusions, loss to follow-up, and missing data. ^aNine subjects submitted no diary (two relocated, three withdrew from the study, and four gave no specific reason). ^bOne subject withdrew after submitting a diary for the untreated attack.

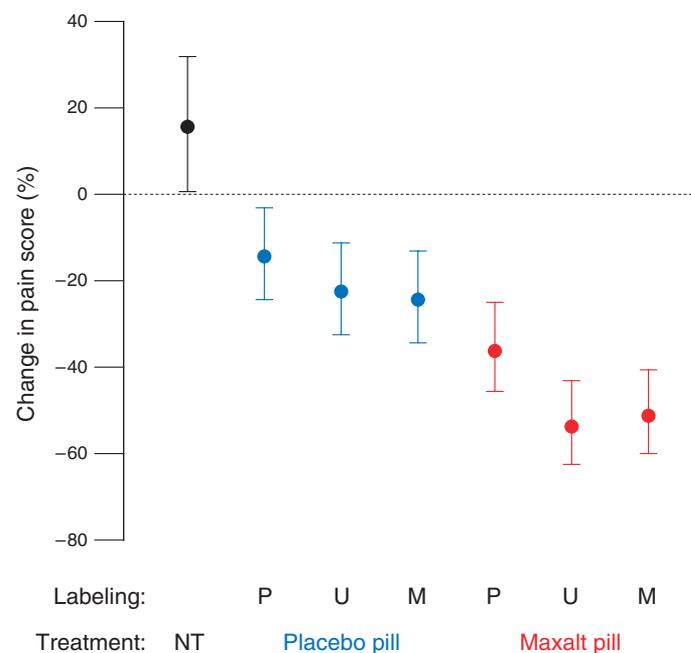


Fig. 3. Changes in headache intensity as a percentage of the 30-min pain score. The data are estimates for the seven experimental conditions, with 95% CIs, from the generalized linear mixed model (table S8). The estimates for the three types of information (labeling) are grouped according to whether the treatment was a placebo pill (blue) or a Maxalt pill (red). The within-subjects design of this study allowed each subject to serve as his or her own control, which substantially increased statistical power. Consequently, 95% CIs cannot be interpreted in the same manner as in a typical between-subjects study. Thus, two groups can differ significantly even when the mean for one group falls within the 95% CI for the other group. NT, no treatment; P, “placebo” label; U, unspecified “Maxalt or placebo” label; M, “Maxalt” label.

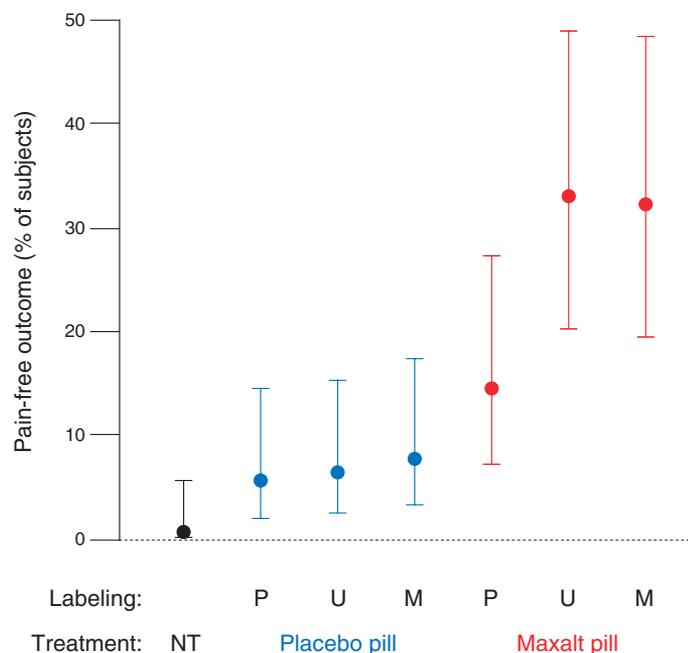


Fig. 4. Percentage of subjects who reported being pain-free 2.5 hours after onset of headache. The data are estimates for the seven experimental conditions, with 95% CIs, from the mixed-effects logistic regression model (table S13). The estimates for the three types of information (labeling) are grouped according to whether the treatment was a placebo pill (blue) or a Maxalt pill (red). NT, no treatment; P, “placebo” label; U, unspecified “Maxalt or placebo” label; M, “Maxalt” label.

DISCUSSION

By manipulating the information provided to patients, our primary analysis showed that the magnitude of headache relief induced by Maxalt (10-mg rizatriptan), as well as that of placebo, was lowest when pills were labeled as placebo, and higher when pills had uncertain labeling or were labeled as active medication. Two other findings were that (i) placebo treatment mislabeled as 10-mg Maxalt reduced headache severity as effectively as did Maxalt mislabeled as placebo, and (ii) open-label placebo treatment was superior to no treatment. We conclude that raising the likelihood of receiving active treatment for pain relief significantly contributed to increased success rate of triptan therapy for migraine, that open-label placebo treatment may have an important therapeutic benefit, and that placebo and medication effects can be modulated by expectancies.

Although Maxalt was superior to placebo under each type of information, we were surprised that the efficacy of Maxalt mislabeled as placebo was not significantly better than the efficacy of placebo mislabeled as Maxalt. We were also surprised to find that open-label placebo treatment induced pain relief as compared with the worsening of pain during the untreated attack. A therapeutic benefit of open-label placebo versus no treatment was also recently reported for patients with irritable bowel syndrome in a randomized controlled study (8) and in a pilot study in depression (9).

One of our exploratory goals was to assess whether information provided to patients can influence the net therapeutic gain of drug treatment (drug efficacy minus placebo efficacy). We found that the

difference in pain-free outcome between Maxalt and placebo was reduced by negative information (9 percentage points) compared with neutral (27 percentage points) or positive information (25 percentage points). The results for the primary endpoint were in the same direction, but less marked (21.6, 30.8, and 26.9 percentage points for negative, neutral, and positive information, respectively). The reduced therapeutic gain when negative information was provided to patients appeared to reflect a decrease in the efficacy of the drug rather than an increase in the efficacy of the placebo treatment, a conclusion supported by a recent imaging study (10). In the context of triptan therapy for migraine, our data suggest that the therapeutic gains cannot be improved by decreasing positive information; in fact, lower expectations may reduce drug-placebo differences.

In the placebo literature, expectancy is usually defined as the subjective probability of the occurrence of a certain clinical outcome (11). Many placebo researchers would have considered our provision of positive, neutral, and negative information as a method for manipulating expectancy (12, 13). However, we did not assess expectancies in our within-subjects experiment because we thought such queries might cause patients to question the accuracy of the information we provided. Therefore, we cannot assert with certainty that our manipulation worked through changes in conscious or nonconscious expectations due to the information provided (14). We also did not assess blinding to avoid suspicions in a within-subjects design. Because our study used deception, its applicability to routine clinical care is limited, and the present findings are essentially a proof of concept. It would be important to expand our findings with experimental manipulations of expectancy considered ethical in clinical practice.

To our knowledge, only one between-subjects study previously examined clinical pain responses of placebo under three different information sets (13). Thoracotomized patients ($n = 38$), all of whom were treated postsurgically with a fixed dose of buprenorphine, also received a basal intravenous infusion of saline solution for the first 3 days after surgery. The patients received three kinds of information concerning the saline: (i) a rehydrating solution (no additional treatment control), (ii) either a powerful medication or placebo (uncertain information), or (iii) a powerful painkiller (positive information). Request for oral pain medication, the primary outcome measure, was lowest with positive information, highest in the no additional treatment condition, and intermediate in the uncertain condition. Our study improved on this previous study by using a within-subjects design, including an uncompromised no-treatment control, and examining both placebo and active treatment responses.

We were surprised that when Maxalt was labeled “Maxalt or placebo,” it had a numerically greater effect on pain (though statistically not significant, $P = 0.385$) than when it was labeled “Maxalt.” We had expected that greater certainty of receiving active medication would result in greater efficacy (as occurred for the placebo experiment described above and the placebo treatment in our experiment). Very few experiments have compared medication under different degrees of certainty. Some have found that certainty increases medication efficacy in pain and anxiety (15, 16), whereas other studies, for example, in Parkinson’s disease (17) and cancer pain (18), have shown that uncertainty enhances medication effects. A related experiment with asthmatic patients showed that positive expectations selectively affected placebo but not drug responses (19). Furthermore, anthropological investigations have noted that patients assessing whether treatment is helpful report that the increased vigilance that

comes with uncertainty may increase therapeutic efficacy (20). This conflicting evidence suggests that much research is needed in this domain.

In conclusion, positive information about active medication contributes to successful treatment of episodic migraine. Medication and information (which presumably influences expectancies) may be equally critical for pain relief. The benefits of placebo persist even if placebo treatment is honestly described. Whether treatment involves medication or placebo, our study clearly shows that the information provided to patients and the predictable ritual of pill taking are important components of care (21). Further research is warranted to investigate the application of our findings to clinical practice and research design.

MATERIALS AND METHODS

Study design

The study followed migraine headache subjects over seven migraine attacks (ClinicalTrials.gov identifier: NCT00719134). Baseline pain intensity in the absence of treatment was measured in an untreated first attack. Then, subjects self-reported response to treatment over the next six attacks, for which they were given one of two treatments (Maxalt or placebo) labeled in one of three ways (Maxalt, placebo, Maxalt or placebo) with labels that were true (for four attacks) or false (for two attacks) (Fig. 1 and Table 1).

Participants

Participants were recruited from Beth Israel Deaconess Medical Center outpatient clinics; they signed an informed consent in a prescreening visit and met with investigators (S.K.-H. and R.B.) to determine eligibility. Participants were eligible if they met the criteria of the International Headache Classification Committee for Migraine (7), had suffered from episodic migraine attacks (with and without aura) in the past 3 years, and were at least 18 years old. Excluded were non-migraine headache, peripheral nervous system injuries, chronic pain conditions, opioid use, cardiovascular or cerebrovascular disorders, cardiac risk factors, or uncontrolled hypertension. Eligible patients were informed that the purpose of the study was to understand the effects of 10-mg rizatriptan (orally disintegrating melting tablet, brand name Maxalt-MLT, Merck and Co. Inc.) and placebo treatment (microcrystalline cellulose, Merck) on acute migraine (Supplementary Methods: Scripted Information Read to Participants).

Medications

At the end of the prescreening visit, each patient received seven sealed white envelopes, one for each successive migraine attack. The envelope for the first attack ("no treatment") contained a five-page diary concerning details of symptomatology and a small brown envelope containing rescue medications (one 10-mg Maxalt and two 220-mg naproxen for relief 2.5 hours after attack onset) (Fig. 1 and Supplementary Methods). Envelopes for the subsequent six attacks contained a four-page diary and two small brown envelopes, one labeled "study drug" (to be taken 30 min after headache onset) and the other "rescue medication" (containing one 10-mg Maxalt and two 220-mg naproxen, to be taken 2.5 hours after headache onset if the study drug was ineffective). Patients were instructed to open only one white envelope at the beginning of each attack, to do so in the exact order indicated on the envelopes (treatments 1 through 6 in sequence), and to call the responsible phy-

sician anytime (S.K.-H.) to report any adverse event or if they had questions. Patients were also told that, if needed, they could use the rescue medications 2.5 hours after the onset of the attack.

Intervention

The study intervention was manipulation of information about study pill identity to assess the effects of that information on treatment efficacy. At the time of study enrollment, patients were informed that the study drug envelope contained 10-mg Maxalt or placebo, that Maxalt is a medication for aborting migraine headache, that it works best when taken 30 min after onset of headache, and that the placebo pill looks and tastes the same as the Maxalt pill but contains no active medication. They were also informed that for the six study migraine attacks after the baseline attack, the brown study drug envelope would be labeled "Maxalt," "placebo," or "Maxalt or placebo" for three randomly ordered pairs of treatments. It was not disclosed to them that two of the six study drug envelopes were labeled incorrectly: one envelope containing a placebo tablet was mislabeled as Maxalt (to maximize placebo effect), and one envelope containing a tablet of Maxalt was mislabeled as placebo (to minimize drug effect). Exemption from full transparency for the two attacks that involved deception was granted by the institutional review board in compliance with the four criteria specified by Federal Regulation 46.116c (<http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.116>) for Protection of Human Subjects (accessed 31 May 2012) because the deception involved minimal additional risk, did not adversely affect the rights and welfare of the patients, was necessary to practically answer an important question, and was followed with a full debriefing at the end of the study.

Randomization

Patients were randomly assigned in blocks of eight to eight sequence patterns that balanced the order of the two treatments and three types of information (Supplementary Methods: Randomization of Treatment and Treatment Labeling; table S5). A table summarizing the randomization scheme for each patient was placed in a sealed envelope and given to the treating physician (S.K.-H.), to be opened in case of unexpected reaction or medical emergency. All study personnel were blind to treatment allocation.

Outcomes

The primary study outcome was the percentage change from baseline in headache intensity 2 hours after treatment using self-reported pain assessments obtained from diary entries that subjects completed during each attack at home. The secondary study outcome was the proportion of patients pain-free 2 hours after treatment. Pain level was assessed on a discrete numerical scale ranging from 0 (no pain) to 10 (maximal pain). Subjects returned completed diaries after each attack.

Statistical analysis

Our statistical analysis, detailed methods, and additional supporting data can be found in Supplementary Materials and tables S6 to S14. Briefly, our main objective was to assess whether the effect on the primary and secondary endpoints differed among the three types of information and whether the effect differed between the two treatments. We also made exploratory comparisons. For the primary endpoint, change in headache intensity from baseline to 2 hours after treatment, we used generalized linear mixed models with a normal random component and a logarithmic link function to analyze the pain scores.

Because the systematic component of the model is on the logarithmic scale, estimates of differences in its parameters translate into estimates of ratios on the pain score scale, which one can interpret as percentage increase or decrease. These approximate ratios of averages are not literally ratios of means (or means of ratios). Phrases such as “typical value” reflect this feature of the analysis; one can interpret “typical values” as similar to means. For the secondary endpoint, the proportion of patients who were free from pain 2 hours after treatment, we used a mixed-effects logistic regression model to analyze the individual dichotomous outcomes. Its systematic component on the log-odds scale yields estimates that translate into odds, probabilities, and ORs. Preliminary analysis of each endpoint verified that the eight sequence patterns had no statistically significant effects on treatment outcomes and no interactions with labeling or with treatment. Seven participant baseline characteristics (age, sex, family history, years of migraine, attacks per month, migraine days per month, triptan history) were potential covariates, but when added jointly to the primary and secondary models, none were statistically significant. In an exploratory manner, we examined several prespecified pairwise comparisons (“Maxalt labeled placebo” versus “placebo labeled Maxalt”; “placebo labeled placebo” versus “no treatment”) and whether the therapeutic gain (the difference between Maxalt and placebo) differed among the information conditions.

To deal with missing data, we compared the background characteristics of participants who provided no data on any treated attack (dropouts) with those of participants who provided some or all data, using *t* tests for continuous characteristics and Fisher’s exact test for dichotomous characteristics; continuous background variables were expressed as mean (SD) or as median and quartiles (when the data were clearly skewed), and missingness from patients who did not contribute any data to the study was considered uninformative. When a pain score 2 hours after treatment was missing because the subject resorted prematurely to rescue medications, the missing value was imputed using either the pain score at 30 min or a subsequent higher pain score. Missing pain scores not associated with premature rescue treatment (for example, the patient fell asleep) were not imputed.

SUPPLEMENTARY MATERIALS

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Methods

Scripted Information Read to Participants

Randomization of Treatment and Treatment Labeling

Missing Data

Analyses of Primary Endpoint—Fitting the Main Model

Analyses of Secondary Endpoint

Table S1. Reasons for excluding 19 of the prescreened subjects.

Table S2. Background characteristics of participants and dropouts.

Table S3. Selected quantiles of nondichotomous background characteristics of the 66 participants.

Table S4. Incidence of missing pain scores and data imputation.

Table S5. Structure of the eight treatment sequences and assignment of subjects to treatment sequences.

Table S6. Distribution of attacks with imputed pain scores and pain freedom at 2.5 hours.

Table S7. Estimates of parameters in the main model for the pain scores including the imputed pain scores at 2.5 hours.

Table S8. Percentage decrease in the estimated average pain score from 30 min to 2.5 hours under the seven experimental conditions (from an analysis that included imputed pain scores at 2.5 hours).

Table S9. Estimates of parameters in the covariate model for the pain scores including the imputed pain scores at 2.5 hours.

Table S10. Estimates of difference (2.5 hours minus 30 min) on the primary endpoint for key contrasts involving treatment and labeling.

Table S11. Sensitivity analysis of the main model for the pain scores.

Table S12. Estimates of parameters in the main model for pain freedom at 2.5 hours.

Table S13. Estimated probability of being pain-free 2 hours after treatment under the seven experimental conditions (from an analysis that included imputed pain scores at 2.5 hours).

Table S14. Estimates of difference (2.5 hours minus 30 min) on the secondary endpoint for key contrasts involving treatment and labeling.

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