



Impact of Headache and Over-the-Counter Treatment on Pain and Functional and Cognitive Parameters: A Real-World Study across Three Geographies

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ABSTRACT

Introduction: Individuals with headache choose over-the-counter (OTC) medications to relieve pain and associated symptoms. This real-world evidence study investigated the effect of three OTC headache treatments on headache intensity and the associated impairment of

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cognitive and functional parameters in headache sufferers in Germany, Brazil, and Japan.

Methods: This prospective, multinational, observational eDiary-based study included adults experiencing headache for ≥ 6 months, with ≥ 2 headache episodes per month requiring treatment and using one of the three OTC headache treatments (Germany: ibuprofen 400 mg+caffeine 100 mg; Brazil: dipyrone 1 g; Japan: ibuprofen 100 mg+caffeine 40 mg). The primary endpoint was change in headache intensity (11-point numeric rating scale [NRS]) from baseline (headache onset) to 2 h post-treatment. Secondary endpoints were association between NRS scores for headache intensity and for cognitive

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and functional parameters and change in these parameters from baseline to 2 h post-treatment.

Results: Of the 32,623 individuals screened, 1239 were enrolled in the study, with 607 having their first headache episode treated using one of the OTC treatments. Baseline demographics and characteristics were similar across the cohorts. At 2 h post-treatment, headache intensity significantly improved, with the mean change from baseline being 3.4 (3.1, 3.7, 95% confidence interval), 4.2 (3.9, 4.5), and 3.0 (2.7, 3.3) for German, Brazilian, and Japanese cohorts, respectively. Improvement was observed in all cognitive and functional parameters. The NRS score for headache intensity significantly predicted NRS scores of all cognitive and functional parameters ($P < 0.0001$).

Conclusions: The study shows that headache intensity significantly affects cognitive and functional aspects, as well as overall quality of life, for sufferers globally. It confirms the effectiveness of OTC medications and suggests using headache intensity as a self-assessment tool for symptom severity, highlighting the need for new parameters in the OTC domain to improve public health benefits.

Keywords: Real-world evidence; Headache; Migraine; Over-the-counter medication; Consumer healthcare

Key Summary Points

Why carry out the study?

There is limited understanding and guidance on how headache intensity affects cognitive and functional aspects and overall quality of life of headache sufferers, particularly upon the use of over-the-counter (OTC) medications.

Various randomized controlled trials have demonstrated the efficacy of these OTC medications; nevertheless, their efficacy may not directly translate into their effectiveness in clinical settings.

What was learned from the study?

This real-world evidence study confirms the role of OTC medications in alleviating headache intensity and their impact on cognitive and functional abilities in a large sample of headache sufferers across Germany, Brazil, and Japan.

The findings of this study highlight the need for new parameters to measure symptom severity for better treatment outcomes in headache sufferers.

INTRODUCTION

Headache disorders present diverse phenotypes, each characterized by distinct clinical features. The International Classification of Headache Disorders (ICHD-3) divides headache disorders into primary and secondary categories, encompassing various headache types including migraine, tension-type headache, and trigeminal autonomic cephalalgias. The classification also includes neuropathies, facial pain, and other specific headache conditions [1]. Altogether, they are one of the most common drivers of disability, affecting 3.1 billion individuals globally [2]; their impact on the patients goes beyond the debilitating pain, as they impair cognitive function [3, 4], productivity [5–7], and overall quality of life (QoL) [4], incurring significant global burden [8] and healthcare costs [9–11]. A multinational descriptive analysis of the real-world burden of headache, which used the “Migraine Buddy” application, revealed that over one-third of 24,763 users experienced up to five episodes of headache or migraine per month, impacting their QoL through impaired concentration, being slower in their daily activities, and missing work or social activities [4].

Headache is one of the most common causes of self-medication worldwide [12, 13] because it is considered a minor ailment [14–16], and the consulting behavior of the sufferers depends on various factors, such as pain intensity, number of accompanying symptoms, disabilities due to headache, and attack frequency [17]. A recent

prospective real-world study reported that 98.3% of the 350 participants used over-the-counter (OTC) analgesics for the treatment of headache symptoms, even after being prescribed medication for headache. Among the most recommended OTC medications for self-management of headache are metamizole (dipyrone) [18, 19], aspirin, acetaminophen (paracetamol), and nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and naproxen [20]. Moreover, combination medications containing caffeine [21], aspirin [22], and acetaminophen [23] are beneficial for some types of headache, particularly tension-type headache [24]. However, their use for the management of headache disorders could vary among countries due to differences in healthcare systems, regulations, and cultural practices [25].

Furthermore, the efficacy of these OTC medications, proven by various randomized controlled trials (RCTs), may not directly translate into their effectiveness in real-life settings. Real-world evidence (RWE) studies complement RCTs by providing insights into treatment effectiveness, safety, and generalizability beyond controlled environments, guiding evidence-based medicine [26]. Moreover, the guidelines for RCTs on headache disorders underscore the importance of secondary assessment of a sufferer's cognitive and functional impairment [27, 28] because these disorders negatively impact "mental clarity," which involves concentration, attention, reading, processing speed, and memory [3, 29]. Most previous studies assessing the effectiveness of OTC medications for cognitive and functional parameters in headache sufferers typically included small sample sizes ranging from 10 to 75 participants [3, 30–32]. This indicates a relative scarcity of RWE on how OTC headache medications directly affect cognitive and functional parameters in headache sufferers.

Considering the above, in the present study, we investigated the effect of three local active pharmaceutical ingredients (APIs) on headache intensity and the associated impairment of cognitive and functional parameters for headache sufferers in three different geographical regions, namely the European Union, Latin America, and Asia. These regions have different healthcare systems and cultural perspectives, which may

influence cognitive and functional outcomes. We included large cohorts of participants experiencing headache in Germany, Brazil, and Japan and assessed the endpoints recommended by the guidelines for RCTs on migraine and tension-type headache [4, 27, 28, 33]. The primary objective was to assess the real-world impact of OTC treatments on headache intensity using the established pain numeric rating scale (NRS) score. The secondary objectives were to describe the association between headache intensity and cognitive and functional parameters, and to describe the real-life impact of OTC treatments on these parameters. The study was reported in its preliminary form at the 16th European Headache Congress (Vienna, Austria, 07–10 December 2022) [34].

METHODS

Study Design

The study was a prospective, multinational, observational study conducted from 27 May 2021 to 17 October 2022. The study (21062-01) was submitted and approved by the US Institutional Review Board (IRB): Ethical and Independent (E&I) Review Services, which is now known as Salus IRB. The study was approved by local ethics committees in Germany, Brazil, and Japan. All participants provided informed consent electronically before initiation of data collection.

Study Population

Potential participants from Germany, Brazil, and Japan were pre-identified by an external vendor (SurveyEngine GmbH; <https://surveyengine.com>), using targeted email campaigns, internet banners, and pop-up ads to recruit a survey panel. The inclusion criteria were as follows: participants aged ≥ 18 years and experiencing headache for ≥ 6 months, with ≥ 2 headache episodes per month requiring treatment; and those using ibuprofen 400 mg + caffeine 100 mg, dipyrone 1 g, or ibuprofen 100 mg + caffeine 40 mg (henceforth referred to as

the OTC treatments) available locally in Germany, Brazil, and Japan, respectively.

The participants who were using other OTC medications for headache were excluded to reduce heterogeneity that would affect multiple other formulations. Those who were currently using prescription medications for headache and/or experiencing headache secondary to a specific illness, such as cold, flu, head injury, or hangover, were also excluded.

The enrolled set consisted of all participants who provided consent and met the study inclusion and exclusion criteria. The eligible set consisted of all enrolled participants who experienced at least one headache episode within 15 days after enrollment, and their pain intensity NRS score was assessed at baseline and 2 h post-treatment on an 11-point scale ranging from 0 to 10 for all the QoL parameters. The full analysis set (FAS) consisted of all eligible participants with a qualifying headache episode, defined as the first headache episode treated with one of the OTC treatments of interest, and their headache intensity NRS score was assessed at baseline and 2 h post-treatment.

Data Collection

The data were collected prospectively using the IMPACT-TED eDiary app. The participants answered the online sign-up survey (participant eDiary provided in Supplementary appendix) to learn about the panel and provide individual or household demographics. The study consisted of the following three periods (Fig. 1): enrollment period (day 1), during which the eligibility criteria were verified; observation period, from day 1 to the day of the first headache episode or a maximum period of 15 days; and the evaluation period, which began on the day of the first headache episode and included the next 14 days (total 15 days), and the data were collected at baseline and at 2 h after taking the OTC headache medication.

The parameters that were recorded at baseline before the administration of any medication included demographics, headache type, headache intensity, pain location, additional headache-related symptoms, cognitive impact, and functional impact. The parameters that were assessed at 1.5–2.5 h post-treatment were medication taken, timing of medication administration, other non-medicinal therapeutic approaches, headache intensity, cognitive

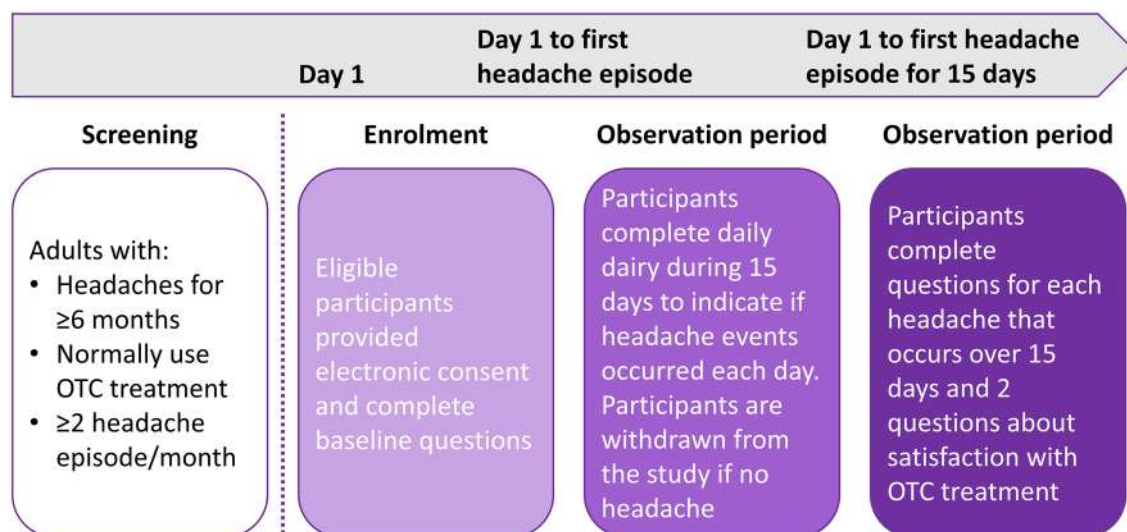


Fig. 1 Study flow chart. *OTC* over-the-counter, *NRS* numeric rating scale. Responders: $\geq 30\%$ decrease in pain intensity NRS score from baseline. Recovery: $\geq 20\%$ improvement in NRS score from baseline to 2 h post-treatment

impact, functional impact, impact on school/work, and impact on daily activities.

Study Endpoints

The primary endpoint was change in headache intensity from baseline (at headache onset) to 2 h post-treatment assessment for the qualifying headache episode (defined as the first episode treated with OTC treatment only), assessed via an 11-point NRS (0=no pain, 10=worst pain imaginable) [27, 28, 35]. The key secondary endpoints (2a) were the associations between headache intensity NRS scores and impact on cognitive and functional parameters, assessed using an NRS (0=no impact, 10=severe impact): QoL components such as ability to concentrate, be attentive, and focus (cognitive parameters); ability to be productive, coordinate multiple activities, and think clearly; and energy (functional parameters) [4]. Other secondary endpoints (2b) included change in impact of headache on the functional and cognitive parameters, which were assessed from baseline to 2 h post-treatment, and the impact of headache on daily activities, including work and school [33], assessed using single-answer (yes/no) questions. The primary and secondary (2b) endpoints were analyzed for the FAS, and secondary (2a) endpoints were analyzed for the eligible set.

Responder Analysis

The participants were considered responders if the change in their headache intensity NRS score from baseline was $\geq 30\%$. For cognitive and functional parameters, the participants were considered responders if the change in their NRS score from baseline was $\geq 20\%$.

Statistical Analysis

In the absence of prior study findings, an effect size (Cohen's *d*) of 0.2 (i.e., a small effect [36]) was targeted as the minimum difference of interest and used for sample size calculation. For each country cohort, a sample size of 199 headache sufferers was required to achieve 80% power with an alpha level of 5% using a paired *t*-test.

To achieve this target, up to 332 headache sufferers were planned to be enrolled in the study (i.e., drop-out rate of 40%). Thus, up to 996 headache sufferers were planned to be enrolled across all three countries.

All data were collected by the participants using an eDiary app in real time via standard data collection measures. Baseline demographics were listed and summarized using descriptive statistics. The pain NRS scores were categorized as severe if the respondent selected a score of 7–10 [35]. NRS scores were treated as continuous data, as is typical for pain studies, although the authors recognize their fundamentally ordinal nature.

For the primary effectiveness endpoint, a paired *t*-test was used to assess the change in mean NRS score at 5% significance level. Between-cohort comparisons were not performed in this study. The associations between cognitive and functional parameters and headache intensity were described using scatterplots, Kendall's tau coefficient, and Kendall's tau independence test. For all secondary endpoint analyses, a linear mixed-effects model was used to account for both baseline covariates as fixed effects, and the repeated observations at the patient and visit levels were used as random effects to assess the mean change in NRS scores. The treatment effects were adjusted on baseline parameters as severity and were confirmed considering these potential drivers.

Sensitivity analyses were conducted to confirm pain response and its effects. The responder/non-responder analysis was performed using binary definitions of response ($\geq 30\%$ for pain intensity) and recovery ($\geq 20\%$ for cognitive and functional parameters) as defined in the responder analysis section.

RESULTS

Overall, 32,623 participants were screened for eligibility. In total, 1239 were included in the enrolled set (426, 361, and 452 from Germany, Brazil, and Japan, respectively). Of these, 880 were included in the eligible set (293, 261, and 326, respectively), and 607 were included in the

FAS (202, 209, and 196, respectively). The main reason for exclusion from the FAS was absence of a headache episode treated only with one of the OTC treatments of interest and lack of assessment of headache intensity NRS score at baseline and 2 h post-treatment (Fig. 2; Supplementary Table 1).

The baseline demographics and characteristics of the participants in the FAS are presented in Table 1. Overall, the mean (SD) age of the participants was 40.8 (10.7) years, which was similar

across the three cohorts. A higher proportion of participants were female, except in the German cohort, where an almost equal number of male and female participants were enrolled. These proportions were consistent with the enrolled and eligible sets (overall and by country). Overall, 91.4% and 73.8% of participants complained of “headache” and “migraine,” respectively. Only 27.2% of participants were diagnosed with a headache by healthcare providers, and “self-decision” was the most common (94.1%) reason for using OTC headache treatments.

At baseline, the overall study population exhibited a mean (95% confidence interval [CI]) pain NRS score of 5.8 (5.6, 5.9). NRS scores were skewed toward moderate and severe pain, with 45.1% of participants reporting an NRS score of 4–6 (moderate pain) and 38.2% reporting an NRS score of ≥ 7 (severe pain). No participants were pain-free at baseline. The mean (95% CI) pain NRS score at baseline was 5.8 (5.6, 6.1), 6.5 (6.3, 6.8), and 4.9 (4.7, 5.2) in the German, Brazilian, and Japanese participants, respectively (Fig. 3). NRS scores were skewed toward moderate (51.0% and 34.4%) and severe pain (35.6% and 56.5%) for German and Brazilian participants, respectively. In the Japanese participants, baseline NRS scores were skewed toward moderate (50.5%) and mild (28.1%) pain.

Primary Endpoint Analysis

At 2 h post-treatment, the mean (95% CI) pain NRS score decreased from 5.8 (5.6, 5.9) to 2.2 (2.1, 2.4), with most participants (77.2%) reporting an NRS score of ≤ 3 . The mean change (95% CI) in pain NRS score from baseline to 2 h post-treatment was 3.6 (3.4, 3.7), indicating a significant improvement in pain ($P < 0.0001$). Improvement in pain NRS scores was observed in the participants from all three countries (Fig. 3). The mean (95% CI) pain NRS score decreased from 5.8 (5.6, 6.1) to 2.4 (2.2, 2.7), from 6.5 (6.3, 6.8) to 2.3 (2.0, 2.7), and from 4.9 (4.7, 5.2) to 1.9 (1.6, 2.2) in the German, Brazilian, and Japanese participants, respectively. A majority of participants reported an NRS score of ≤ 3 (74.2%, 75.6%, and 82.1% for Germany, Brazil, and Japan, respectively). The mean change

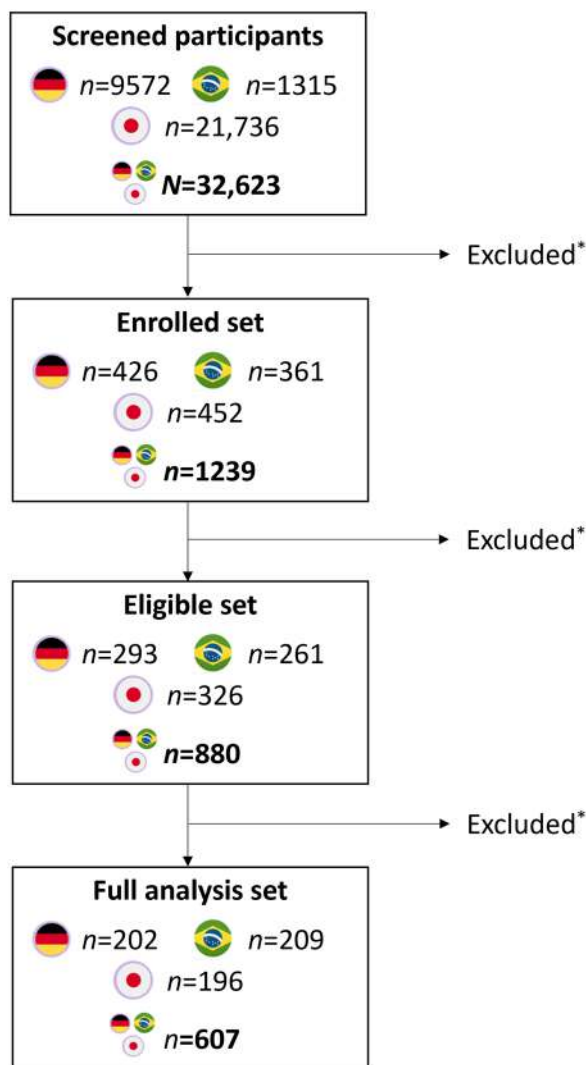


Fig. 2 Flowchart describing participants' disposition. *N* represents the total number of participants screened and *n* represents the cohorts. *Reasons for exclusion are detailed in Supplementary Table 1

Table 1 Demographics and characteristics of participants in the full analysis set

Characteristic	FAS			
	Germany <i>n</i> = 202	Brazil <i>n</i> = 209	Japan <i>n</i> = 196	Overall <i>n</i> = 607
Mean (SD) age, years	42.8 (12.0)	37.8 (9.2)	41.9 (10.2)	40.8 (10.7)
Female, <i>n</i> (%)	102 (50.5)	163 (78.0)	142 (72.4)	407 (67.1)
Employment status, <i>n</i> (%)				
Employed full-time	142 (70.3)	100 (47.8)	105 (53.6)	347 (57.2)
Employed part-time ^a	29 (14.4)	51 (24.4)	39 (19.9)	119 (19.6)
Not currently employed	7 (3.5)	42 (20.1)	41 (20.9)	90 (14.8)
Student	4 (2.0)	6 (2.9)	5 (2.6)	15 (2.5)
Retired	20 (9.9)	3 (1.4)	2 (1.0)	25 (4.1)
Time period experiencing headache, <i>n</i> (%)				
6 months to 1 year ago	17 (8.4)	38 (18.2)	1 (0.5)	56 (9.2)
≥ 1 year to < 2 years ago	32 (15.8)	82 (39.2)	9 (4.6)	123 (20.3)
≥ 2 years ago	153 (75.7)	89 (42.6)	186 (94.9)	428 (70.5)
Type of headache usually experienced (self-reported), <i>n</i> (%)				
Headache	200 (99.0)	203 (97.1)	152 (77.6)	555 (91.4)
Migraine	127 (62.9)	151 (72.2)	170 (86.7)	448 (73.8)
Unknown	3 (1.5)	1 (0.5)	11 (5.6)	15 (2.5)
Diagnosis of headache by healthcare provider, <i>n</i> (%) (%), yes	82 (40.6)	31 (14.8)	52 (26.5)	165 (27.2)
Headache frequency, <i>n</i> (%)				
Less than once per week	23 (11.4)	17 (8.1)	41 (20.9)	81 (13.3)
Once per week	73 (36.1)	61 (29.2)	63 (32.1)	197 (32.5)
Twice per week	67 (33.2)	60 (28.7)	50 (25.5)	177 (29.2)
Three times per week	29 (14.4)	35 (16.7)	24 (12.2)	88 (14.5)
More than three times per week	10 (5.0)	36 (17.2)	18 (9.2)	64 (10.5)
Reason for using local OTC headache treatments, <i>n</i> (%)				
Doctor prescription	18 (8.9)	15 (7.2)	2 (1.0)	35 (5.8)
Pharmacist's recommendation ^a	125 (61.9)	97 (46.4)	20 (10.2)	242 (39.9)
Relative's recommendation	102 (50.5)	133 (63.6)	40 (20.4)	275 (45.3)
Self-decision	191 (94.6)	193 (92.3)	187 (95.4)	571 (94.1)
Publicity	72 (35.6)	124 (59.3)	171 (87.2)	367 (60.5)
Other	11 (5.4)	12 (5.7)	12 (6.1)	35 (5.8)

^a39 or fewer hours per week

FAS full analysis set, OTC over-the-counter, SD standard deviation

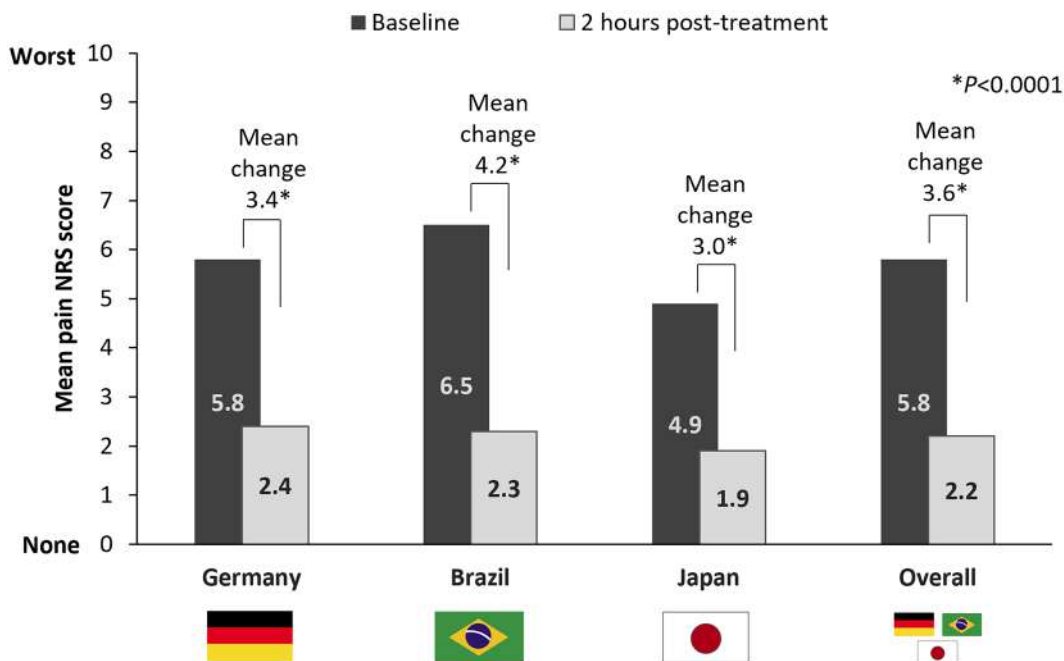


Fig. 3 Mean value and mean change in pain numeric rating scale (NRS) scores from baseline to 2 h post-treatment for participants from Germany, Brazil, and Japan in the full analysis set, considering that the first headache episode was treated using one of the over-the-counter (OTC) treat-

ments of interest. [†]Change was calculated as NRS score at baseline minus NRS score at 2 h post-treatment. Positive change score indicates improvement in pain. *From paired *t*-test

(95% CI) in pain NRS score from baseline to 2 h post-treatment was 3.4 (3.1, 3.7), 4.2 (3.9, 4.5), and 3.0 (2.7, 3.3) for German, Brazilian, and Japanese participants, respectively, indicating a significant improvement in pain (all $P < 0.0001$) (Fig. 3).

Overall, 24.4% of participants reported no more pain (NRS score=0) at 2 h post-treatment. In the German, Brazilian, and Japanese cohorts, 17.3%, 29.7%, and 26.0% of participants, respectively, reported no pain at 2 h post-treatment.

Secondary Endpoint Analyses

At baseline, Kendall's tau coefficient revealed a significant ($P < 0.0001$) correlation between all cognitive and functional parameters and headache intensity in all participants. At 2 h post-treatment, a significant association was observed between headache intensity and all parameters

among German and Japanese participants. For Brazilian participants, a significant association was observed between the ability to concentrate and the ability to focus (Fig. 4; Supplementary Table 2).

In the FAS, the mean changes in pain NRS scores from baseline to 2 h post-treatment for cognitive and functional parameters ranged from 3.5 to 3.6 and from 3.4 to 3.8 in German participants; 3.6–3.7 and 3.7–3.9 for Brazilian participants, and 3.2–3.3 and 3.4–3.6 for Japanese participants, respectively. A significant ($P < 0.0001$) improvement was observed for all cognitive and functional parameters from baseline to 2 h post-treatment (Fig. 5).

At 2 h post-treatment, the number of episodes with moderate-to-severe impact (NRS score: 7–10) on all cognitive and functional parameters was reduced from that at baseline among all participants. Across all seven parameters, the proportion of participants reporting recovery of optimal functional and cognitive parameters

with pain relief (NRS score=0) was 25–30% in all three country cohorts; 80–90% of participants reported a mild impact (NRS score < 5) after 2 h of treatment.

The participants reported that their headache episodes ($n=1718$) resulted in inability to attend (11.8% of total episodes) and/or impaired performance (34.2% of total episodes) at work/school. Headache episodes were also associated with missed social activities (30.1% of total episodes) and family time (23.9% of total episodes), inability to use electronic devices (39.5% of total episodes), slower performance of home duties (61.4% of total episodes), and inability to function (30.6% of total episodes). The participants who rated their headache as “severe” reported greater impact on work/school activities (Supplementary Table 3).

Sensitivity Analyses

A responder/non-responder analysis of associations between categorized NRS pain scores and changes from baseline to 2 h post-treatment revealed that >80% of participants in each of the three cohorts experienced $\geq 30\%$ reduction in headache intensity from baseline and were defined as “responders.” Among the responders, >91% achieved meaningful ($\geq 20\%$) improvement in all functional and cognitive parameters from baseline across all three cohorts (Supplementary Table 4).

There were 510 NRS pain responders; among this responder group, over 93% had recoveries in the seven cognitive and functional measures. Reduction in severity of impact was observed across all parameters in all three cohorts.

DISCUSSION

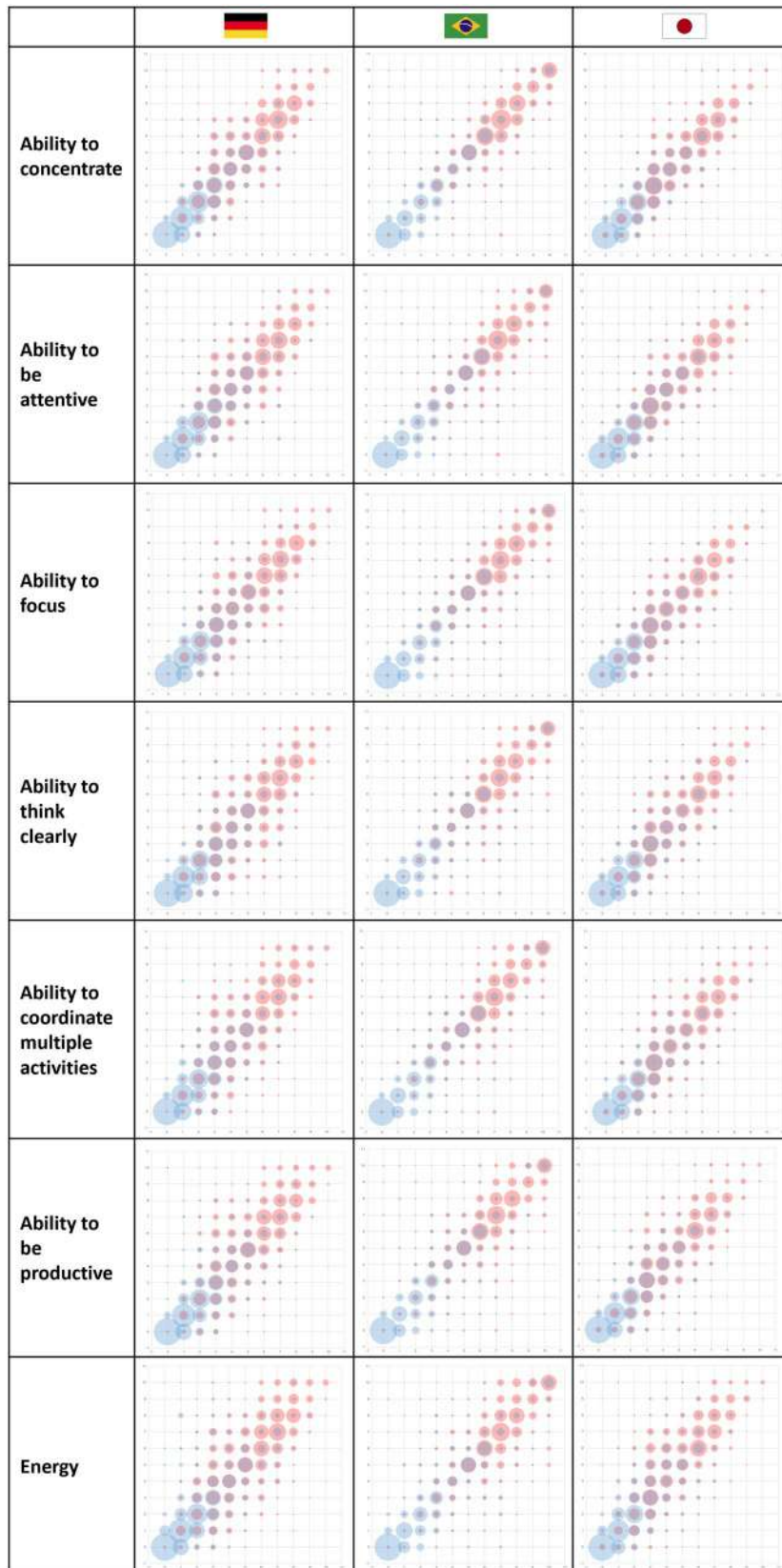
In the present study, the participants reported impairment of all assessed cognitive and functional parameters before taking the OTC medications, and the impairment was correlated with headache intensity. Furthermore, the medications significantly reduced headache intensity

and positively impacted all cognitive and functional parameters of the participants.

Additionally, the association between reduction in headache intensity and improvement in cognition and overall functioning confirmed that headache intensity was a significant predictor of all cognitive and functional parameters; an almost one-to-one relationship was also observed between headache intensity NRS score and the seven QoL parameters. All cognitive (three) and functional (four) parameters were significantly improved, with headache intensity treatment exhibiting the maximum positive impact on the participants' ability to concentrate (cognitive) and energy (functional).

The findings of our study are consistent with the results from previous real-world and randomized studies and build on a growing evidence base, revealing the added impacts of headaches and benefits of OTC treatments. A recent 12-week-long, single-arm RWE study, based on data from wearable activity trackers and questionnaires, reported that headache has a significant negative impact on daily life and activity [17]; it also reported that OTC pain relievers are the preferred treatment choice of people experiencing headache and that self-treatment decisions are highly influenced by symptom severity [17].

A prospective, randomized, crossover study reported that the cognitive performance of individuals decreases during migraine attacks, particularly reading and processing speed, verbal memory, and learning [3]. Furthermore, an open-label, single-attack study including 28 people with acute migraine reported that sumatriptan injection 6 mg during the attack improved impaired cognitive functioning [31, 37]. Two other studies that investigated the impact of headache on cognitive performance reported an association between headache intensity and cognitive function [30, 32]. However, these studies reported conflicting opinions regarding whether the negative impact of headache intensity on cognitive function is dependent on the type of task being performed. Moore et al. concluded that headache intensity impairs general task performance, irrespective of the task complexity [32], whereas Attridge et al.



◀**Fig. 4** Scatterplots showing the relationship between pain intensity numeric rating scale (NRS) score and cognitive and functional parameter NRS scores at baseline (red) and 2 h post-treatment (blue) in the eligible set in German, Brazilian, and Japanese cohorts (from left to right). On each scatterplot, the pain intensity NRS score is shown on the *x*-axis, and the functional/cognitive parameter NRS score is shown on the *y*-axis. Each axis ranges from -1 to 11

concluded that the effect of headache intensity is dynamic, even within a given type of pain [30].

Furthermore, this real-world study including participants from Germany, Brazil, and Japan reported similar responses across all geographies, despite the cultural differences and variability in approaches to assessing and treating headache. This suggests that the relationship between headache intensity and the cognitive parameters is ubiquitous and independent of culture-specific behaviors or influences, indicating scope for generalizability of our results to these three as well as other countries.

Strengths and Limitations

This is the first real-world study to confirm the effect of the most widely available OTC medications on headache intensity and on cognitive and functional parameters in a large sample of headache sufferers. The study design is based on the available guidelines for conducting controlled trials on migraine and tension-type headache [27, 28] due to the lack of specific recommendations for conducting RWE studies in this therapeutic area. The NRS scores clinically validated for the assessment of headache intensity are intuitive for headache sufferers and have well-established cross-cultural utility [38]. In the present study, we aimed to scale the assessment of impacts on cognitive and functional parameters to the established assessment of headache perception by anchoring to the validated pain impact scale, thereby demonstrating the relationships between reduction of headache and impact on these parameters and providing evidence in support of the hypothesis that these

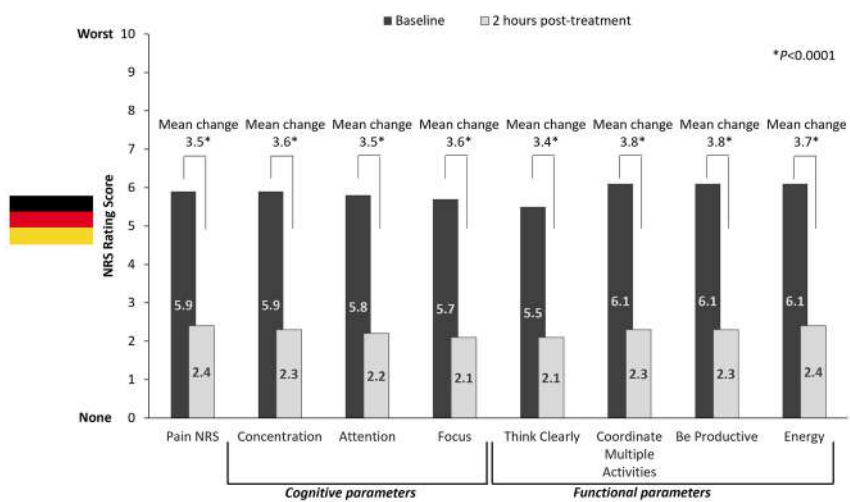
are due to a true effect (as opposed to a placebo effect).

For predefined analyses, NRS scores were treated as a continuous variable. This is consistent with the results of major randomized trials that have used NRS pain scores as primary outcome measures [39, 40]; however, we acknowledge that this could be considered interpretation bias. Nevertheless, the findings of the sensitivity analysis, conducted on a categorical basis, as well as the responder/non-responder sensitivity analysis supported the findings of the main analyses. Our responder definitions were based on those typically used in chronic disease; the definitions are therefore conservative when applied to the benefits of treatment for an acute condition, such as headache. However, although the responses were assessed just 2 h post-treatment, meaningful pain relief was observed in $\geq 80\%$ of participants.

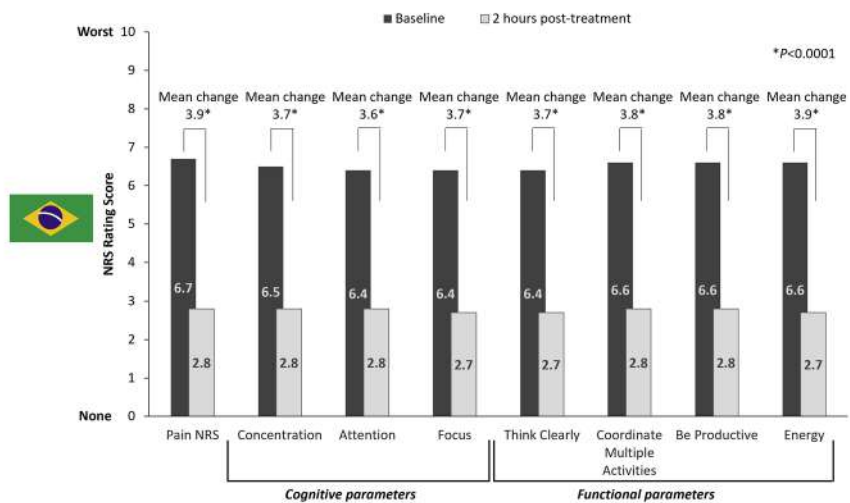
As anticipated for this type of digital study conducted in a real-world setting [41] and as outlined in Table 1, the delay between recruitment and active participation affected dropout rates. This highlights the difficulty in recruiting participants who meet the eligibility criteria to form a representative consumer panel, subsequently causing delays in achieving the desired sample size. Furthermore, including only those with > 1 attack per month may have also contributed to the dropouts.

In addition, the included participants may not be representative of the general population in each country, and since the study involved the use of an eDiary app, the inclusion of participants may have been biased in ways that are not apparent from the summarized demographic data, i.e., selection of participants with greater affinity for technology. However, the inherent sampling limitations [42] of the web-based survey were not deemed to significantly affect our conclusions, owing to the enhanced suitability and user-friendliness of digital apps for evaluating pain impact and related lifestyle factors [43]. No attempts were made to corroborate the participant-reported data. This was because only the participants could accurately record their experiences and the impact of OTC treatment on headache intensity and cognitive and functional parameters. Moreover, external

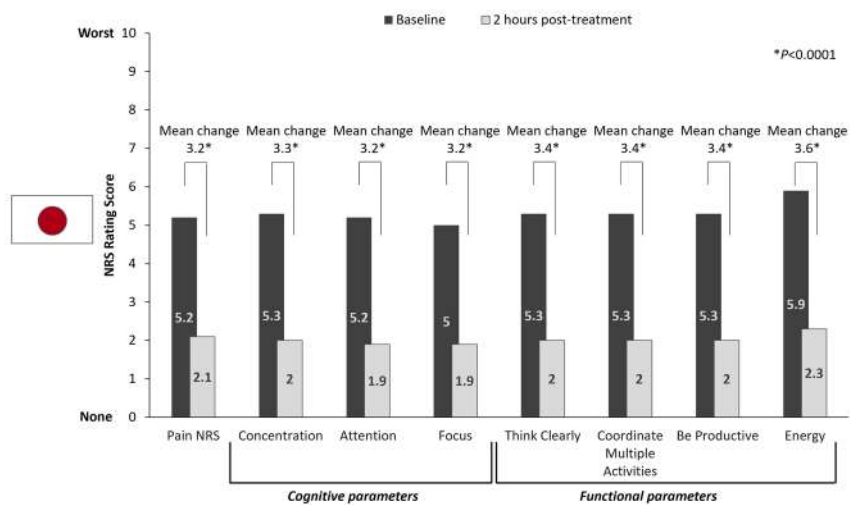
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b



c



◀**Fig. 5** Cognitive and functional parameters assessed before and after headache treatment, considering all headache episodes were treated using one of the over-the-counter (OTC) treatments of interest among the participants in the full analysis set from (A) Germany ($n = 495$ episodes), (B) Brazil ($n = 746$ episodes), and (C) Japan ($n = 477$ episodes). NRS, numeric rating scale

verification of reported data was not considered to be appropriate or valid.

Another possible limitation is that the full analysis used only the first headache episode reported during the 15-day evaluation period, which was treated using one of the OTC medications. However, all headache episodes during the 15-day period in the enrolled set were considered for secondary analyses, and the improvement in headache intensity and in the cognitive and functional parameters were reported for those episodes. Another limitation is that the responses were only assessed at one time point post-treatment (1.5–2.5 h), and thus the timing of headache relief was not evaluated. Although this study reports a high level of headache relief at 2 h post-treatment, suggesting that headache relief was initiated prior to this time point, further studies should be performed to identify the initiation point of headache relief.

Moreover, cognitive and functional categories were defined based on prior medical feedback; NRS was used due to the unavailability of any other tool to assess the parameters included in this real-world study. This emphasizes the need for an objective assessment of these parameters, by measuring performance in a test paradigm. Furthermore, treatment benefits could not be confirmed by headache type due to the variability in the index event experienced by the participants. Most participants in Germany and Brazil reported general headache, whereas those in Japan reported both general headache and migraine. Moreover, differences were observed in the percentage of participants diagnosed with headache by healthcare providers from each country (Germany: 40.6%; Brazil: 14.8%; Japan: 26.5%), which could be attributed to various OTC headache treatments or societal and/or healthcare system differences.

The parameters assessed in this study could serve as a self-administered and disease-related outcome tool to measure the severity of symptoms that impact functional and cognitive parameters in individuals experiencing headache; thus, they could be included in future studies to define the QoL of individuals experiencing headache.

CONCLUSION

This study highlights the significant impact of headache intensity on cognitive and functional aspects and on the overall QoL for headache sufferers. The results emphasize the role of OTC medications in managing headaches, based on data from a large sample of individuals with headache in Germany, Brazil, and Japan, which consequently impact clinical practice by highlighting patient preferences for accessible treatments, revealing risks like medication-overuse headache, and guiding clinicians to tailor treatment strategies. Moreover, the study suggests that headache intensity could be used as a self-administered tool to measure symptom severity, underscoring the need for new parameters in the OTC domain to improve public health outcomes for headache sufferers, which could lead to better treatment strategies and outcomes.

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Data Availability. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Peter J. Goadsby reports, over the last 36 months, personal fees from Sanofi; grant from Kallyope, and personal fees from Aeon Biopharma, AbbVie, Aurene, CoolTech LLC, Dr Reddy's, Eli Lilly and Company, Linpharma, Lundbeck, Pfizer, PureTech Health LLC, Satsuma, ShiraTronics, Teva Pharmaceuticals, Tremeau, and Vial; personal fees for advice from Gerson Lehrman Group, Guidepoint, SAI Med Partners, and Vector Metric; fees for educational materials from CME Outfitters; and publishing royalties or fees from

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