

# Patient-Reported Outcome in Two Chronic Diseases: A Comparison of Quality of Life and Response Profiles in Severe Migraine and Severe Asthma

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Christian Lucas<sup>1</sup>  
Samia Aly<sup>2</sup>  
Chantal Touboul<sup>3</sup>  
Rahma Sellami<sup>3</sup>  
Xavier Guillaume<sup>3</sup>  
Gilles Garcia<sup>4</sup>

<sup>1</sup>Centre d'Evaluation et de Traitement de la Douleur, Service de Neurochirurgie, Hôpital Salengro, CHRU de Lille, Lille, France; <sup>2</sup>Novartis Pharma, Rueil-Malmaison, France; <sup>3</sup>Kantar, Montrouge, France; <sup>4</sup>Service de Pneumologie, Hôpital Bicêtre, CHU Paris Sud, Kremlin-Bicêtre, France

**Introduction:** Migraine and asthma are two frequent, disabling, chronic disorders with a major impact on patient well-being. The objectives of this study were to compare subjective well-being between patients with severe forms of migraine or asthma using a panel of PROs.

**Methods:** Adult patients were recruited during routine consultations with chest physicians or neurologists. Patients with severe migraine (reporting headaches on  $\geq 8$  days/month and having failed  $\geq 2$  prophylactic treatments) and patients with severe asthma (according to the 2017 GINA definition: requiring Step 4 or 5 treatment or presenting uncontrolled symptoms) were eligible. Each patient completed the EuroQol Questionnaire (EQ-5D-5L), the Work Productivity and Activity Impairment Questionnaire (WPAI) and the Hospital Anxiety and Depression scale (HAD). Patients with severe migraine the 6-item Headache Impact Test (HIT-6) and those with severe asthma completed the Asthma Control Test (ACT).

**Results:** 249 patients with severe migraine and 96 with severe asthma were enrolled. Mean EQ-5D-5L utility scores were significantly higher in the severe migraine group than in the severe asthma group ( $0.75 \pm 0.25$  vs  $0.68 \pm 0.26$ ;  $p < 0.01$ ). Low EQ-5D-5L utility scores were associated with frequent ( $\geq 15$  headache days/month) or disabling (HIT-6 score  $\geq 60$ ) headaches and with poor asthma control. Patients with severe migraine more frequently presented a HAD depression score  $\geq 11$  (23.0% in severe migraine; 7.5% in severe asthma;  $p < 0.01$ ), whereas those with severe asthma more frequently reported problems with mobility, self-care and usual activities. Absenteeism (percent worktime missed) was similar in both groups (severe migraine:  $9.0\% \pm 19.1\%$ ; severe asthma:  $13.8\% \pm 22.9\%$ ) but work impairment was higher in the severe migraine group (44.3% vs 28.4%;  $p < 0.01$ ).

**Conclusion:** Quality of life, work activity and psychological distress are all deteriorated in both severe migraine and severe asthma. Different aspects are affected in the two diseases: a greater impact on psychological aspects in severe migraine and a greater impact on physical aspects in severe asthma.

**Keywords:** quality of life, work performance, psychological distress, asthma, migraine

Correspondence: Christian Lucas  
Centre d'Evaluation et de Traitement de la Douleur, Service de Neurochirurgie, Hôpital Salengro, CHRU de Lille, Lille, France  
Tel +33 3 20 44 60 76  
Email christian.lucas@chru-lille.fr

## Introduction

Patient-reported outcome measures (PROMs) are designed to measure patient perceptions of their health and illness. These measures are important in routine clinical practice for gaining insight into how diseases affect general well-being and how these perceptions evolve over time. In clinical trials, they are important to

measure the impact of treatments and disease management strategies on health perceptions. From a public health perspective, they are important in determining the burden of disease and for informing health policies and notably in prioritising the provision of health services.

Patient-reported outcome measures fall into two classes, generic measures and disease-specific measures. Generic PROMs, such as the Short-Form 36-item health profile (SF-36),<sup>1</sup> its shorter derivative the Short-Form 12-item health profile (SF-12),<sup>2</sup> the Sickness Impact Profile,<sup>3</sup> the Nottingham Health Profile<sup>4</sup> and, more recently, the EuroQoL five dimension questionnaire (EQ-5D)<sup>5</sup> have been developed. These are useful for comparing health perceptions between different diseases. Specific PROMs are intended to determine health status in particular diseases and, as such, are designed to be highly sensitive to changes in functional domains that are specific for particular diseases (such as motor function in stroke patients). In common chronic diseases, such as migraine<sup>6</sup> and asthma,<sup>7</sup> large numbers of specific PROMs have been developed over the past three decades, spawning an abundant literature. For example, in migraine, the Migraine-Specific Quality of Life Questionnaire<sup>8</sup> and 6-item Headache Impact Test (HIT-6)<sup>9</sup> are well established and validated. In asthma, the Asthma Quality-of-Life Questionnaire<sup>10</sup> and the Asthma Control Test (ACT)<sup>11</sup> have been validated and used widely.

Comparing findings between the many studies that have used generic PROMs to evaluate perceived health status in individual diseases is complicated by methodological differences between studies, such as the context of the study, the source population, how patients were selected and how the PROMs were administered. For this reason, studies which compare PROM scores between different diseases using an identical methodology are more informative. In spite of this, there are relatively few within-study comparisons that have been published. A landmark study published over twenty years ago<sup>12</sup> compared the health status of patients measured with the SF-36 between eleven diseases and demonstrated marked differences in overall health perceptions, as well as in the impact on the different health dimensions of the questionnaire. Since then, other studies have compared health perceptions between different diseases, for example multiple sclerosis and Parkinson's disease,<sup>13</sup> epilepsy versus angina pectoris, rheumatoid arthritis, asthma and chronic obstructive pulmonary disease,<sup>14</sup> different dermatological diseases<sup>15</sup> or diabetes and asthma.<sup>16</sup>

The objectives of this study were to assess and compare quality of life (QoL), work performance and psychological distress using a panel of PROMs between two groups of patients with one of two frequent, disabling chronic diseases: severe migraine and severe asthma. The rationale behind the choice of these two diseases is related to the recent introduction of new prophylactic treatments for severe migraine.<sup>17</sup> However, there is currently no consensus definition for severe migraine and the indication for these new treatments is an ad hoc one. On the other hand, a consensus definition of severe asthma was introduced by the Global Initiative for Asthma (GINA) over twenty years ago,<sup>18</sup> and the most recent formulation of the concept<sup>19</sup> is over a decade old. In addition, international practice guidelines have recommended severity-based treatment strategies since 2014.<sup>20</sup> For this reason, there is extensive information on the relationship between patient perceptions of the impact of asthma, documented with different PROs, and asthma severity as defined by GINA. It is therefore of interest to evaluate whether the ad hoc definition of severe migraine corresponds to a similar level of patient-perceived impact as the accepted consensus definition of severe asthma.

## Methods

This study was performed in a sample of patients consulting a specialist (neurologists or chest physicians) for severe migraine or severe asthma in France between 24th April and 22nd June 2018.

## Severity definitions

Severe migraine is defined as having at least 8 days of migraine headache per month and to have failed at least two prophylactic treatments. Severe asthma is defined according to the 2017 GINA guidelines as “asthma that is uncontrolled despite adherence with maximal optimized therapy and treatment of contributory factors, or that worsens when high dose treatment is decreased”.<sup>21</sup>

## Recruitment of Physicians

Physicians were identified by random selection from a listing of practicing neurologists and chest physicians in France. Potential participants were recruited by telephone and were administered a screening questionnaire to validate that they fulfilled the eligibility criteria for this study. Specialists working in either hospital or community practice were eligible. Physicians were eligible to participate if they spent  $\geq 60\%$  of their professional activity seeing

patients, had at least three years of specialist experience. Physicians were required to have around fifty percent of their patients having severe migraine or asthma and consulting regularly. This requirement was set in order to optimise the chances of recruiting the required number of patients with severe disease in each diagnostic group during the two-month recruitment period of the study.

Neurologists were required to see at least twenty patients with migraine in a typical month, of whom ten should present with severe migraine (defined as having at least 8 days of migraine headache per month) and should have failed at least two prophylactic treatments. Five of these patients should have episodic migraine (defined as 8–14 days of migraine per month) and five have chronic migraine (defined as  $\geq 15$  days of migraine per month). Chest physicians were required to be specialists in the treatment of severe asthma and to see at least twenty patients with asthma in a typical month, of whom ten should present severe asthma.

## Recruitment of Patients

Each participating physician was expected to invite the next ten patients consulting consecutively during the two-month recruitment period and fulfilling the eligibility criteria to participate in the study. Patients under eighteen years of age, patients presenting another chronic invalidating disease and patients participating in any clinical study were excluded.

Patients with severe migraine were eligible if they had a physician-ascertained diagnosis, reported at least eight migraine days per month (MMD) and had failed at least two prophylactic treatments belonging to different therapeutic classes. Eligible patients were divided into episodic migraine (8–14 MMD) and chronic migraine ( $\geq 15$  MMD) subgroups.

Patients with severe asthma were eligible if they had a physician-ascertained diagnosis of severe asthma according to the 2017 GINA guidelines<sup>21</sup> and had not presented an exacerbation of asthma requiring a short course of oral corticosteroids in the previous month.

## Data Collection

For each patient included, the physician completed a standardised medical questionnaire describing the demographic and clinical features of included patients, which enabled the eligibility criteria to be verified. Each patient enrolled completed an eight-page questionnaire including the five-level EQ-5D-5L,<sup>5</sup> the Work Productivity and Activity Impairment (WPAI) Questionnaire<sup>22</sup> and the

Hospital Anxiety and Depression (HAD) scale.<sup>23</sup> In addition, patients with migraine completed the HIT-6<sup>9</sup> and those with asthma the ACT.<sup>11</sup>

The EQ-5D-5L assesses five aspects of QoL (mobility, self-care, usual activities, pain or discomfort and depression or anxiety) on five-point Likert scales. The profile of responses is converted into a linear, continuous utility measure ranging from  $-1$  to  $1$ . Since no valuation set for the EQ-5D-5L was available at the time the study was conducted, utility values for the EQ-5D-5L were derived from the existing EQ-5D-3L valuation set with the cross-walk method using a validated mapping function,<sup>24</sup> as recommended by NICE. In addition, a visual analogue scale (EQ-5D VAS) rates overall perception of QoL on a linear scale, yielding a score ranging from 0 (worst health the respondent can imagine) to 100 (best health the respondent can imagine).

The WPAI contains six items relating to health problems interfering with work or daily activities over the previous week: one yes/no question (are you currently employed [working for pay]?), three questions on the number of hours missed from work for different reasons and two questions on impact of health problems on work each rated on a ten-point ordinal scale. The WPAI yields four scores (absenteeism, presenteeism, work productivity loss and activity impairment), which can range from 0 (no impact on work/activities) to 100 (total incapacity). The HAD is a fourteen-item questionnaire assessing severity of symptoms of anxiety and depression, seven items relating to anxiety and seven to depression and each scored on a four-point Likert scale. Possible scores for each pathology dimension range from 0 to 21, with a higher score reflecting greater severity. A score over eight on either score corresponds to possible anxiety or depression and a score of  $\geq 11$  on either score corresponds to probable anxiety or depression.<sup>25</sup>

The HIT-6 is a six-item questionnaire, which yields an impact score on a linear scale with minimum and maximum possible values of 36 and 78, respectively. On the basis of this score, subjects can be assigned to one of four impact grades (little or no impact, moderate impact, substantial impact and severe impact). The ACT is a questionnaire containing five items on symptoms or functioning in the previous four weeks, each rated on a five-point Likert scale. The total score can range from 5 (poor control of asthma) to 25 (complete control of asthma), with higher scores reflecting greater asthma control. An ACT score  $> 19$  indicates well-controlled asthma.

All questionnaires were used in their validated French translations.

## Statistical Analysis

The target sample size was established a priori in order to obtain a precision of  $\leq 10\%$  (95% confidence intervals) for the different scores to be measured. In order to achieve this, 100 patients needed to be included in each patient group. For severe asthma, the recruitment target was set at 100 patients. For severe migraine, the recruitment target was set at 250 patients, in order to have 100 patients with chronic migraine, based on the distribution of migraine severity and frequency that has been described in France.<sup>26</sup>

Regarding missing data, if none of the PRO questionnaires were completed in full, the patient was considered non-analysable. For the PRO questionnaires, if any of the items was not scored, the questionnaire was considered failed and was not analysed.

The presentation of the data is purely descriptive and no a priori hypotheses were tested. Continuous data are presented as mean values  $\pm$  standard deviations (SD) or median values. Categorical variables are presented as frequency counts with percentages. Categorical and continuous variables were compared between groups using the  $\chi^2$  test and Student's *t*-test respectively. For the comparison between the distribution of response levels of the EQ-5D, the highest levels (4 and 5 or 3, 4 and 5) were combined when necessary to avoid empty cells or cells containing only one subject. All statistical analyses were performed using Quantum software version 5.8 (IBM, Armonk, United States).

## Ethical Considerations

The survey was conducted in accordance with the ESOMAR International Code on Market and Social Practice, the EphMRA Code of Conduct, relevant current French and European legislation, and Good Epidemiological Practice guidelines. Since the patients' identity did not appear on the study questionnaires and patient management was not affected by participation in the study, submission to an Institutional Review Board for ethical approval was not required. The physicians were required to give a letter of information to their patients who in turn were asked to provide oral consent to their physician before being able to take part in the survey. The letter of information included a summary of the recommendations of the French Data Protection Authority (Commission Nationale de l'Informatique et des Libertés; CNIL) on the protection of personal data and the processing of the data from the survey. Using a dedicated hotline, patients

also had access to all data concerning them as well as the right to correct or delete such data, in conjunction with Kantar Health. To guarantee complete confidentiality, data collection, processing and analysis were centralised by Kantar Health.

## Results

### Participants

Nineteen neurologists (thirteen hospital-based and six community-based) and ten chest physicians (nine hospital-based and one community-based) participated in the study. These physicians recruited 250 patients with severe migraine and 100 with severe asthma. Data for one patient with severe migraine and four with severe asthma were not analysed as none of the PRO questionnaires were completed. The sociodemographic characteristics of the remaining analysable patients (249 with severe migraine and 96 with severe asthma) are presented in [Table 1](#). For both disease groups, the mean age was similar, around 42 years, whereas women were more represented in the severe migraine group than in the severe asthma group ( $p < 0.001$ ). Mean BMI was somewhat lower ( $p < 0.01$ ) in the severe migraine group compared to the severe asthma group. No significant difference in any of these variables was observed between the patients with episodic migraine or with chronic migraine. Around half of the patients with severe asthma were registered for long-term disability status qualifying them for full health insurance coverage, whereas this was only the case for less than ten percent of patients with migraine. In both diseases, the mean time since diagnosis was around twenty years. The mean HIT-6 impact score in patients with severe migraine was 63.7, being higher in the patients with chronic migraine compared to episodic migraine. The mean ACT score in the severe asthma group was 14.5, being higher in controlled than in uncontrolled patients. The number of days in the previous month that patients took sick leave was lower in the severe migraine group than in the severe asthma group ( $p < 0.05$ ).

### Quality of Life

According to the EQ-5D-5L utility measures, mean scores were significantly higher in the severe migraine group than in the severe asthma group ( $p < 0.01$ ; [Table 2](#)). Within the severe asthma group, the mean EQ-5D-5L utility score was higher in the patients with well- or partly controlled asthma than in those with uncontrolled asthma ( $0.83 \pm 0.22$  versus  $0.59 \pm 0.25$ ;  $p < 0.01$ ). Within in the severe migraine group, mean scores were higher in patients with episodic migraine than in those with chronic migraine ( $p < 0.01$ ; [Table 2](#)) and

**Table I** Sociodemographic and Clinical Characteristics of the Study Population

|   | <b>All Severe Asthma<br/>[N = 96]</b> | <b>Episodic Migraine<br/>[N = 170]</b> | <b>Chronic Migraine<br/>[N = 79]</b>       | <b>All Severe Migraine<br/>[N = 249]</b> |
|---|---------------------------------------|--|--|--|
| Age (years)<br>Mean $\pm$ SD                          | 42.2 $\pm$ 16.4                       | 41.8 $\pm$ 13.6                        | 42.7 $\pm$ 12.9                            | 42.1 $\pm$ 13.3                          |
| Gender<br>Women                                       | 57.3%                                 | 75.9%                                  | 77.2%                                      | 76.3%**                                  |
| Educational level                                     | Missing: 1                            | Missing: 2                             |  | Missing: 2                               |
| High school or secondary                              | 29.5%                                 | 20.8%                                  | 19.0%                                      | 20.2%                                    |
| High school graduate                                  | 48.4%                                 | 51.2%                                  | 62.0%                                      | 54.7%                                    |
| University/College education                          | 22.1%                                 | 28.0%                                  | 19.0%                                      | 25.1%                                    |
| Body mass index (kg/m <sup>2</sup> )<br>Mean $\pm$ SD | 25.7 $\pm$ 4.1**                      | Missing: 1<br>23.0 $\pm$ 3.7           | 23.8 $\pm$ 3.9                             | Missing: 1<br>23.3 $\pm$ 3.8             |
| Smoking status<br>Current or previous                 | Missing: 1<br>26.3%                   | Missing: 5<br>32.1%                    | Missing: 2<br>29.9%                        | Missing: 7<br>31.4%                      |
| Long term disability status                           | Missing: 1<br>53.7%**                 | Missing: 2<br>6.6%                     | Missing: 6<br>6.9%                         | Missing: 8<br>6.6%                       |
| Disease duration (in years)<br>Mean $\pm$ SD          | Missing: 4<br>20.6 $\pm$ 16.0         | Missing: 10<br>17.5 $\pm$ 11.9         | Missing: 4<br>19.7 $\pm$ 11.6              | Missing: 14<br>18.2 $\pm$ 11.8           |
| ACT score<br>Mean $\pm$ SD                            | Missing: 4<br>14.5 $\pm$ 4.2          |  |  |  |
| >19 (well-controlled)                                 | 9.8%                                  |  |  |  |
| 16–19 (partly controlled)                             | 28.2%                                 |  |  |  |
| <16 (uncontrolled)                                    | 62.0%                                 |  |  |  |
| Exacerbations in previous year<br>At least one        | Missing: 3<br>80.7%                   |  |  |  |
| Mean number $\pm$ SD (when at least one)              | 3.8 $\pm$ 3.3                         |  |  |  |
| Migraine symptoms for each headache                   |                                       |  |  |  |
| Unilateral localisation                               |                                       | Missing: 1<br>42.0%                    | Missing: 1<br>35.9%                        | Missing: 2<br>40.1%                      |
| Pulsatile   |                                       | Missing: 4<br>44.6%                    | Missing: 1<br>48.7%                        | Missing: 5<br>45.9%                      |
| Aggravation by effort                                 |                                       | Missing: 6<br>57.9%                    | 64.6%                                      | Missing: 5<br>60.1%                      |
| Avoidance of routine activities                       |                                       | Missing: 3<br>46.1%                    | Missing: 1<br>56.4%                        | Missing: 4<br>49.4%                      |
| Nausea or vomiting                                    |                                       | Missing: 4<br>26.5%                    | Missing: 2<br>37.7%                        | Missing: 6<br>30.0%                      |
| Photophobia or phonophobia                            |                                       | Missing: 1<br>48.5%                    | Missing: 1<br>65.4% <sup>†</sup>           | Missing: 2<br>53.9%                      |
| Headache intensity                                    |                                       |  |  |  |
| Mild  |                                       | Missing: 4<br>9.0%                     | Missing: 3<br>2.6%                         | Missing: 7<br>7.0%                       |
| Moderate  |                                       | 46.4%                                  | 43.4%                                      | 45.5%                                    |
| Severe  |                                       | 44.6%                                  | 54.0%                                      | 47.5%                                    |
| HIT-6 score<br>Mean $\pm$ SD                          |                                       | Missing: 3<br>62.9 $\pm$ 5.2           | Missing: 1<br>65.5 $\pm$ 5.3 <sup>††</sup> | Missing: 4<br>63.7 $\pm$ 5.4             |
| $\leq 49$ (little or no impact)                       |                                       | 0.6%                                   | None                                       | 0.4%                                     |

(Continued)



**Table 1** (Continued).

|  | All Severe Asthma<br>[N = 96]   | Episodic Migraine<br>[N = 170]                | Chronic Migraine<br>[N = 79]     | All Severe Migraine<br>[N = 249]               |
|--|---------------------------------|---|----------------------------------|--|
| 50–55 (moderate impact)<br>56–59 (substantial impact)<br>≥60 (severe impact)   |                                 | 7.2%<br>14.4%<br>77.8%                        | 1.3%<br>3.8%<br>94.9%            | 5.3%<br>11.0%<br>83.3%                         |
| Sick leave due to illness (working respondents)<br>Mean number of days ± SD  | Missing: 5<br>14.5 ± 54.0*      | Missing: 19<br>2.8 ± 6.3                      | Missing: 7<br>4.4 ± 7.9          | Missing: 26<br>3.3 ± 6.8                       |
| Consultations for asthma/migraine<br>Every 3 months or more often<br>Every 3 to 6 months<br>Every 6 to 12 months<br>Less than yearly | 30.2%<br>47.9%<br>17.7%<br>4.2% | Missing: 2<br>14.9%<br>55.4%<br>22.0%<br>7.7% | 19.0%<br>57.0%<br>20.3%<br>3.8%  | Missing: 2<br>16.2%*<br>55.9%<br>21.4%<br>6.5% |
| Emergency visits in previous year  | Missing: 5<br>46.2%             | Missing: 1<br>14.8%                           | Missing: 2<br>27.3% <sup>†</sup> | Missing: 3<br>18.7%**                          |
| Use of a prophylactic treatment  | 99.0%                           | Missing: 4<br>81.3%                           | Missing: 3<br>90.8%              | Missing: 7<br>84.3%**                          |

**Note:** \* $p < 0.05$  all severe asthma vs all severe migraine (\*\* $p < 0.01$ ); <sup>†</sup> $p < 0.05$  chronic migraine vs episodic migraine (<sup>††</sup> $p < 0.01$ ).

**Abbreviations:** ACT, asthma control test; HIT-6, six-item headache impact test; SD, standard deviation.

lower in those with a severe impact (HIT-6 score  $\geq 60$ :  $0.72 \pm 0.26$ ) compared to those with a HIT-6 score  $< 60$  ( $0.86 \pm 0.16$ ;  $p < 0.01$ ).

With regard to the EQ-5D VAS score, similar patterns were observed between the different patient groups, although the difference between the severe migraine and the severe asthma group was no longer significant (Table 2). The patterns of response to the different items of the EQ-5D-5L differed between the severe asthma and severe migraine groups (Figure 1), with the former reporting more frequent problems with mobility ( $p < 0.001$ ), self-care ( $p < 0.001$ ) and, marginally, for usual activities ( $p = 0.046$ ), and patients with severe migraine marginally reporting more frequent pain/discomfort ( $p = 0.035$ ) and anxiety/depression ( $p = 0.05$ ). The only difference in the distribution of ED-5Q response modalities between the chronic and episodic migraine groups was observed for the anxiety/depression dimension ( $p = 0.014$ ).

## Work Performance and Impairment

The level of absenteeism (time off work due to health problems) in the last week was similar in patients with severe migraine ( $9.0\% \pm 19.1$ ) and in those with severe asthma ( $13.8\% \pm 22.9$ ). In contrast, presenteeism (time at work when performance was impaired by health problems), work productivity loss and overall activity impairment were

all significantly higher in patients with severe migraine than in those with severe asthma (Table 2).

## Psychological Distress

In both patients with severe migraine and those with severe asthma, mean anxiety scores were relatively high ( $> 8$ ; Table 2) and around 30% in both groups had scores considered indicative of clinical anxiety ( $\geq 11$ ). No difference was observed in mean anxiety scores between these two groups, although the categorical distribution was marginally different ( $p = 0.04$ ), suggesting more frequent anxiety in patients with migraine. The mean anxiety score was significantly higher in patients with chronic severe migraine than in those with episodic severe migraine but the categorical score distribution did not differ significantly according to headache frequency.

For the depression measure, mean scores were lower than the mean anxiety scores, but were significantly higher ( $p < 0.01$ ) in patients with severe migraine (6.9) than in those with severe asthma. The categorical distribution also differed significantly between the two groups ( $p < 0.001$ ), with the proportion of patients with scores consistent with clinical depression being higher in patients with severe migraine (23.0% versus 7.5% in severe asthma). Within the severe migraine group, mean depression scores and the proportion of patients with scores  $\geq 11$  were significantly higher in patients

**Table 2** Summary of Patient-Reported Outcomes

|  | <b>All Severe<br/>Asthma [N = 96]</b> | <b>Episodic<br/>Migraine<br/>[N = 170]</b> | <b>Chronic Migraine<br/>[N = 79]</b>        | <b>All Severe<br/>Migraine [N = 249]</b> |
|--|---------------------------------------|--|---|--|
| <b>EQ-5D</b>   |                                       |  |   |  |
| Utility score (mean $\pm$ SD)  | Missing: 4<br>0.68 $\pm$ 0.26         | Missing: 1<br>0.77 $\pm$ 0.24 <sup>†</sup> | Missing: 3<br>0.70 $\pm$ 0.28               | Missing: 4<br>0.75 $\pm$ 0.25*           |
| VAS score (mean $\pm$ SD)  | Missing: 2<br>63.3 $\pm$ 18.3         | 71.6 $\pm$ 17.5 <sup>†</sup>               | Missing: 1<br>63.9 $\pm$ 21.8               | Missing: 1<br>69.1 $\pm$ 19.3*           |
| <b>WPAI</b>  |                                       |  |   |  |
| Currently in employment  | Missing: 3<br>50.5%                   | 60.6%                                      | 62.4%                                       | 57.0%                                    |
| Hours missed due to health (mean $\pm$ SD)                                       | 3.7 $\pm$ 6.3                         | Missing: 5<br>3.4 $\pm$ 11.4               | Missing: 4<br>4.5 $\pm$ 9.1                 | Missing: 9<br>3.8 $\pm$ 10.8             |
| Hours missed (other) (mean $\pm$ SD)   | 1.6 $\pm$ 5.9                         | Missing: 6<br>5.0 $\pm$ 13.0               | Missing: 4<br>3.4 $\pm$ 8.1                 | Missing: 10<br>4.5 $\pm$ 11.8            |
| Hours worked (mean $\pm$ SD)   | Missing: 6<br>34.2 $\pm$ 11.6         | Missing: 9<br>33.1 $\pm$ 10.2              | Missing: 6<br>32.7 $\pm$ 9.6                | Missing: 15<br>33.0 $\pm$ 10.0           |
| Impact on work productivity (mean $\pm$ SD)                                      | Missing: 3<br>2.8 $\pm$ 2.0           | Missing: 9<br>4.1 $\pm$ 2.4                | Missing: 4<br>5.2 $\pm$ 2.5 <sup>†</sup>    | Missing: 13<br>4.4 $\pm$ 2.5**           |
| Impact on regular activities (mean $\pm$ SD)                                     | Missing: 5<br>3.3 $\pm$ 2.0           | Missing: 4<br>4.8 $\pm$ 2.4                | Missing: 2<br>5.7 $\pm$ 2.5 <sup>††</sup>   | Missing: 6<br>5.1 $\pm$ 2.5**            |
| Absenteeism - Percent work time missed due to problem (mean % $\pm$ SD)          | Missing: 5<br>13.8 $\pm$ 22.9         | Missing: 12<br>7.9 $\pm$ 19.3              | Missing: 8<br>11.6 $\pm$ 18.7               | Missing: 20<br>9.0 $\pm$ 19.1            |
| Presenteeism - Percent impairment while working due to problem (mean % $\pm$ SD) | Missing: 3<br>28.4 $\pm$ 20.0         | Missing: 9<br>41.2 $\pm$ 23.7              | Missing: 4<br>51.5 $\pm$ 25.2 <sup>††</sup> | Missing: 13<br>44.3 $\pm$ 24.5**         |
| Work productivity loss (mean % $\pm$ SD)   | Missing: 6<br>36.5 $\pm$ 25.9         | Missing: 15<br>44.6 $\pm$ 25.2             | Missing: 8<br>56.8 $\pm$ 27.4 <sup>†</sup>  | Missing: 23<br>48.1 $\pm$ 26.4*          |
| Activity impairment (mean % $\pm$ SD)  | Missing: 5<br>33.1 $\pm$ 20.2         | Missing: 4<br>47.7 $\pm$ 24.4              | Missing: 2<br>57.3 $\pm$ 25.2 <sup>††</sup> | Missing: 6<br>50.7 $\pm$ 25.0**          |
| <b>HAD</b>   |                                       |  |   |  |
| Anxiety score  | Missing: 2                            |  | Missing: 1                                  | Missing: 1                               |
| Mean $\pm$ SD  | 8.1 $\pm$ 4.2                         | 8.0 $\pm$ 3.7                              | 9.2 $\pm$ 4.4 <sup>†</sup>                  | 8.4 $\pm$ 4.0                            |
| $\leq 7$ (anxiety absent)  | 51.1%                                 | 43.5%                                      | 32.0%                                       | 39.9%*                                   |
| 8–10 (doubtful anxiety)  | 18.1%                                 | 31.8%                                      | 30.8%                                       | 31.5%                                    |
| $\geq 11$ (clinical anxiety)   | 30.8%                                 | 24.7%                                      | 37.2%                                       | 28.6%                                    |
| Depression score   | Missing: 2                            |  | Missing: 1                                  | Missing: 1                               |
| Mean $\pm$ SD  | 4.9 $\pm$ 3.5                         | 6.3 $\pm$ 3.9                              | 8.1 $\pm$ 4.5 <sup>††</sup>                 | 6.9 $\pm$ 4.2**                          |
| $\leq 7$ (depression absent)   | 81.9%**                               | 60.6%                                      | 44.9% <sup>†</sup>                          | 55.6%**                                  |
| 8–10 (doubtful depression)   | 10.6%                                 | 21.8%                                      | 20.5%                                       | 21.4%                                    |
| $\geq 11$ (clinical depression)  | 7.5%                                  | 17.6%                                      | 34.6% <sup>††</sup>                         | 23.0%                                    |

**Notes:** \* $p < 0.05$  all severe asthma vs all severe migraine (\*\* $p < 0.01$ ); <sup>†</sup> $p < 0.05$  chronic migraine vs episodic migraine (<sup>††</sup> $p < 0.01$ ).

**Abbreviation:** SD, standard deviation.

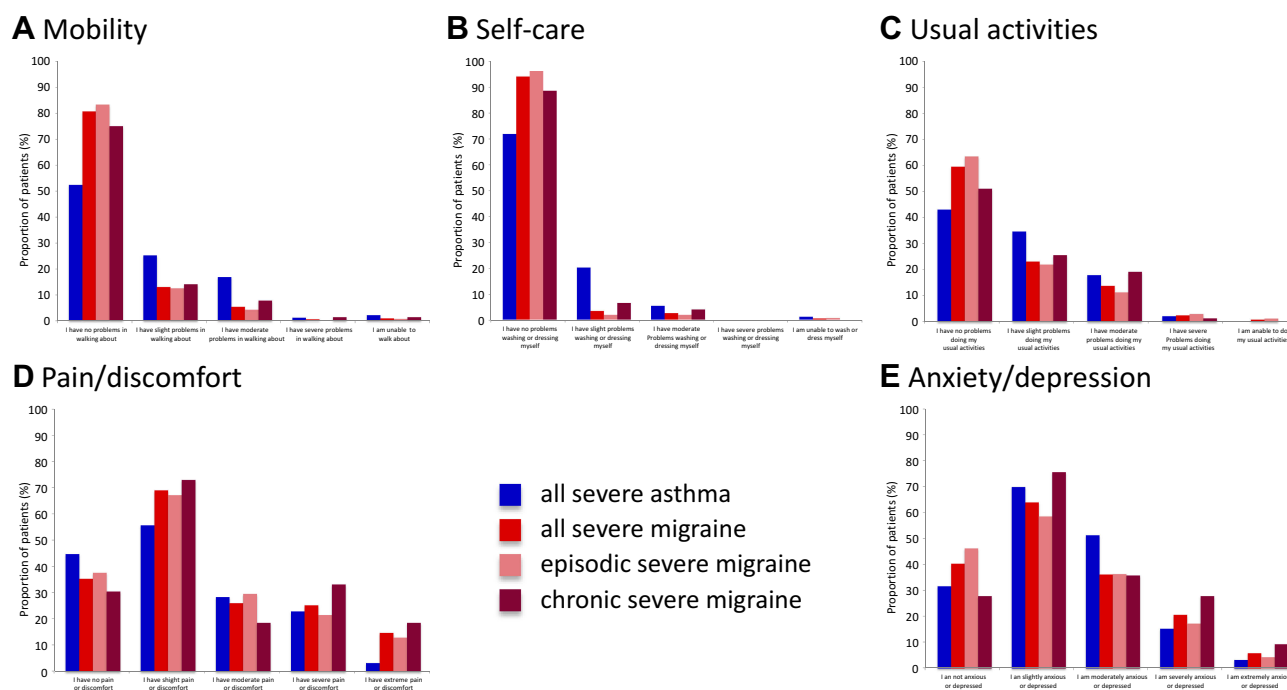
with chronic headaches compared to those with episodic headaches ( $p < 0.01$  in both cases).

## Discussion

This study of PROMs in patients with severe migraine and severe asthma has shown that both these conditions are associated with deteriorations in quality of life, although the pattern of deterioration differs between the

two. Mean EQ-5D utility scores were 0.68 in severe asthma and 0.75 in severe migraine, compared to 0.89 in the French general population.<sup>27</sup> The minimally important clinical difference for the EQ-5D-5L has been estimated to be in the range of 0.04–0.07.<sup>28</sup>

In the severe migraine group, mean EQ-5D utility scores were significantly lower (worse QoL) in patients with chronic rather than episodic migraine and in the former group, the



**Figure 1** Responses to individual items of the EQ-5D. (A) Mobility. (B) Self-care. (C) Usual activities. (D) Pain/Discomfort. (E) Anxiety/Depression.

mean EQ-5D utility score was 0.70, close to the score in patients with severe asthma. Similarly, scores were lower in patients reporting a severe impact with the HIT-6. The difference in mean EQ-5D scores between chronic and episodic migraine was 0.07, the minimally important clinical difference on this measure.<sup>28</sup> Similarly, in the severe asthma group, mean scores were significantly lower in patients with uncontrolled asthma than in those with well- or partly controlled severe disease, the difference again being larger than the minimally important difference, consistent with other studies.<sup>29</sup> The relationships observed between headache frequency and impact or asthma control, on the one hand, and QoL on the other are consistent with those reported in other studies in these diseases<sup>29–34</sup> and provide further support for the internal validity of these PROMs for evaluating patients with severe migraine or severe asthma.

In the case of severe migraine, the mobility, self-care and usual activity items of the EQ-5D were less impacted than in severe asthma, whereas the converse was true for the pain/discomfort item. Using the HAD, which measures psychological distress, mean scores on the depression item were significantly higher in severe migraine than in severe asthma, and 23% of subjects with severe migraine had scores consistent with clinically relevant depression compared to 7% of the subjects with severe asthma. In contrast, scores on the anxiety dimension of the HAD were similar in the two groups.

With regard to work performance measured with the WPAI, absenteeism over the past week was relatively low in both severe migraine (9.0%) and severe asthma (13.8%). In contrast, presenteeism, work productivity loss and impact impairment all affected around one-half of potential work/activity time in severe migraine and around one-third of this time in severe asthma. This impact was consistently higher in chronic than in episodic migraine. It should be noted that the definition of severe migraine required patients to experience on average eight headaches a week (fifteen headaches a week for chronic migraine) and that the diagnostic criteria for migraine specify that migraine headaches may last from 4 to 72 hrs and are aggravated by or cause avoidance of routine physical activity.<sup>35</sup> For this reason, it is to be expected that the amount of time when activities are impaired by migraine headaches will be high.

The PROM scores observed in this study are generally consistent with those observed in previous studies of asthma<sup>16,29,36</sup> and migraine<sup>32,37,38</sup> in France. However, since the present sample consists of patients with severe disease only, absolute EQ-5D scores were lower, and WPAI and HID scores higher, than in studies evaluating patients with asthma or migraine of undifferentiated severity.

It is important to note that the differences observed in PROM scores between severe migraine and severe asthma are subject to a risk of confounding due to other variables



that may be distributed differently between the two patient groups and which may influence the quality of life or other constructs evaluated. Possible such confounding factors include age, gender and disease severity. Mean age was close between the two disease groups. The proportion of female patients was, as expected, higher in the severe migraine group than in the severe asthma group. However, women tend to rate their quality of life lower than do men,<sup>27</sup> and confounding by gender would thus tend to bias the findings towards worse quality of life in severe migraine, the reverse of what was actually found. The presence of other confounding factors cannot be excluded.

The strengths of this study include the relatively large number of patients included, the range of PROMS used and the limited amount of missing data. In addition, patients were enrolled by specialists experienced in migraine or asthma, who confirmed the diagnosis and ascertained disease severity. The principal limitation was that the samples of severe migraine and severe asthma patients were not matched and that, for this reason, potential confounding factors cannot be excluded. In addition, no control group was included and absolute disutilities associated with severe migraine and severe asthma cannot be determined.

With regard to severity, the definition of severe asthma was based on the GINA definition whereas that used for severe migraine was an ad hoc one and thus somewhat arbitrary. It is thus possible that other definitions of severe migraine would have yielded different findings, and this would be of interest to explore in future studies, notably to evaluate whether the impact of migraine is primarily driven by headache intensity or headache frequency, or both. In this respect, it has recently been proposed that the definition of chronic migraine be broadened from  $\geq 15$  headache days with at least eight MMD to only  $\geq 8$  MMD.<sup>39</sup> The motivations for this proposal were first that patients with  $\geq 15$  headache days per month and those with  $\geq 8$  but  $< 15$  headache days are essentially the same and secondly that the burden of disease is high in both groups. These were the two severe migraine groups evaluated in the present study. Our findings study partially support the proposal as no differences between the two groups were found in terms of demographic characteristics, symptom presentation, sick leave or physician consultations. On the other hand, EQ-5D quality of life scores, WPAI work impairment scores and HAD psychological distress scores all indicated more impact of migraine in the patients with  $\geq 15$  MMD compared to those with  $\geq 8$  but  $< 15$  MMD. It would be interesting to evaluate whether disease impact, measured with such scales, varies linearly with headache frequency or whether there is a clear

inflection point which could be used to define chronic or severe migraine.

In conclusion, quality of life, work activity and psychological distress are all deteriorated both in severe migraine, notably in chronic disease, and in severe asthma, but different aspects are affected in the two diseases. The different PROMs used in this study provide consistent information on the impact of these diseases on the patient.

## Data Sharing Statement

The data are hosted by a third party (Kantar Health). Access to the data will require special permission. Reasonable requests can be made to the corresponding author, who will transfer the request to the database manager.

## Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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## Disclosure

Dr Christian Lucas reports personal fees from Novartis, during the conduct of the study; personal fees from Lilly, personal fees from Amgen, personal fees from Ethypharm, grants and personal fees from Sanofi, personal fees from Teva, personal fees from Grunenthal, personal fees from Biogen, and personal fees from Boston Scientific, outside the submitted work. Prof. Dr. Gilles Garcia reports personal fees from Novartis, during the conduct of the study; personal fees from GSK, AstraZeneca, Roche, Sanofi, and MSD, outside the submitted work. Mrs Samia Aly is an employee of Novartis. Mrs Chantal Touboul, Mrs Rahma Sellami and Mr Xavier Guillaume are employees of Kantar Health. Mrs Chantal Touboul and Mr Xavier Guillaume report personal fees from Novartis, during the conduct of the study. The authors report no other conflicts of interest in this work.

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