The Burden of Chronic Urticaria from Brazilian Patients’ Perspective

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ABSTRACT

Introduction: Chronic urticaria (CU), a proxy for chronic spontaneous urticaria, has been associated with a negative impact on health-related quality of life (HRQoL) and costs, but there is limited evidence on the burden of CU in Brazil. The objective of this study was to estimate the prevalence of CU and assess the burden of CU on HRQoL and healthcare resource utilization (HRU) among adults in Brazil.

Methods: This retrospective, cross-sectional study, pooled data from the 2011, 2012, and 2015 National Health and Wellness Survey in Brazil (n = 36,000). Respondents (aged ≥18 years) diagnosed with and treated for CU provided data on demographics, health history, HRQoL (mental and physical health status) on Short-Form SF-36v2, presence of psychological complaints, work impairment, activity impairment, and HRU. Generalized linear models, controlling for covariates, examined differences between those treated for CU and matched controls on the outcome variables.

Results: The prevalence of diagnosed CU was 0.41% (n = 249) and treated CU was 0.21% (n = 127). After adjustments, CU (currently treated for CU) was associated with worse mental functioning, physical functioning, and health utilities compared with controls (all p < 0.01). CU had over twice the odds of anxiety and sleep disturbances, over 1.5 times the work and activity impairment, twice the number of total physician visits, eight times the number of allergist visits, and twice the number of emergency room visits as controls (all p < 0.01).

Conclusions: Many CU patients using prescription treatment experienced anxiety and sleep disturbances, poorer HRQoL, significant work and activity impairment, and high HRU, compared with matched general population controls. Findings suggest an unmet need for more effective treatment and management of CU in Brazil.

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INTRODUCTION

Urticaria is a disease characterized by wheals (hives), which are accompanied by itching or burning sensations, and/or angioedema [1]. When these symptoms last at least 6 weeks, the disease is considered chronic [2]. Chronic urticaria (CU) can be classified into chronic spontaneous/idiopathic urticaria (CSU/CIU) and chronic inducible urticaria [1, 2]. CU has no identifiable trigger, and symptoms and signs can be unpredictable [1, 2]. The peak incidence is between 20 and 40 years of age, and prevalence is higher among women than men [3–9]. The average duration of CU is generally 1–5 years, but varies from a few months to well over a decade [3].

The point prevalence of CU has been estimated to range from 0.1 to 1.0% [4, 10], with recent studies reporting the diagnosed prevalence of CU to be 0.53% in the United States (US) [5] and 0.63% across five major European countries [6].

Although not life threatening, CU, including CSU/CIU, has been associated with a negative impact on different aspects of patients’ health-related quality of life (HRQoL) [11]. For example, previous research found this condition related to an increased prevalence of anxiety and depression [5, 6, 12], greater impairment in work and daily activities, and with negative consequences on healthcare providers and society [5, 6, 12, 13]. Furthermore, patients with urticaria tend to report higher overall work productivity impairment than those with pruritus or psoriasis, as well as higher classroom productivity impairment than those with atopic dermatitis or eczema [14].

Despite its substantial impact on patient HRQoL and social costs, the prevalence of CU and evidence about the economic and humanistic burden associated with CU in the Brazilian population is limited. Thus, the objectives of this research study were to assess the prevalence and the burden of illness, as defined by HRQoL, psychological complaints, work impairment, impairment or disruption of non-work activities, and the use of healthcare resources, among the adult Brazilian population who self-reported current treatment for CU (used as a proxy for CSU).

METHODS

Study Design and Sample

This study was a retrospective, cross-sectional analysis, using an existing database of survey responses from the National Health and Wellness Survey (NHWS) in Brazil. The NHWS includes questions asking about the experience, diagnosis, and treatment of chronic hives (CU), which we used as a close approximate for CSU (accordingly, going forward, we refer to chronic hives as CU). Using CU as a proxy for CSU is consistent with the approach employed by previous studies with NHWS data [5, 6, 15]. Further, more than two-thirds of cases of CU can be classified as CSU (estimates ranging between 66% and 93%) [3]. Potential respondents of the NHWS were identified primarily through participation in opt-in online survey panels, with stratified random sampling within the survey panel to ensure representativeness of the Brazilian population in terms of age and gender. The current project used data collected in 2011, 2012, and 2015 (the NHWS did not collect data in 2013 and 2014 in Brazil). Respondents were required to be at least 18 years of age, able to understand Portuguese, and provide informed consent. All procedures performed in studies involving human participants were in accordance with the ethical standards of the Essex Institutional Review Board (Lebanon, NJ, USA), and the Pearl Institutional Review Board (Indianapolis, IN, USA), and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent was not required.

Measures

Chronic Urticaria

The proportions of the adult Brazilian population in the NHWS who reported having ever experienced CU, reported a physician diagnosis...
of CU, and reported current treatment for this condition were individually evaluated. Respondents who reported current treatment were compared with controls (i.e., those who did not report ever experiencing chronic hives). Respondents who had either experienced or were diagnosed with the condition, but not currently being treated, were excluded from the analyses.

**Sociodemographics and General Health Characteristics**

Several sociodemographic characteristics were assessed in the NHWS: age, sex, race, employment status (yes/no), annual household income (below median vs. above median vs. decline to answer), marital status (married or living with partner vs. not), level of education (university education or higher vs. less than a university education), and type of health insurance (public vs. private). Socio-economic status was also assessed using a reference measure developed by the Associação Brasileira de Anunciantes, Associação Brasileira dos Institutos de Pesquisa de Mercado, and Associação Nacional de Empresas de Pesquisa de Mercado [16]. According to this classification, social classes are stratified as a function of household comfort (presence of electronic equipment, cars, and housekeeper) and the level of education of the head of the household. Based on the total punctuation (from 0 to 46), there are eight levels of socio-economic classification (A1: 42–46 points; A2: 35–41 points; B1: 29–34; B2: 23–28; C1: 18–22; C2: 14–17; D: 8–13 and E: 0–7) [16]. Also, body mass index (BMI) was calculated from self-reported height and weight and categorized as underweight (<18.5 kg/m²), normal weight (18.5 to <25.0 kg/m²), overweight (25.0 to <30.0 kg/m²), obese (30.0 kg/m² and above), or decline to answer. Cigarette smoking (current vs. former vs. never), frequency of alcohol use (none vs. less than daily vs. daily), and whether the respondent reported vigorous exercise in the past 30 days (yes vs. no) were measured. To assess comorbid burden, respondents answered questions from the Charlson Comorbidity Index (CCI) [17]. The CCI sums and weights the presence of several different diseases and disorders, such that the greater the total index score, the greater the comorbid burden on the patient.

**HRQoL**

Health status was assessed in 2010 and 2011 using questions from the Medical Outcomes Study 12-Item Short Form Survey Instrument Version-2 (SF-12v2), which is a multipurpose, generic health status instrument comprised of 12 questions; the longer SF-36v2 was used in the 2015 NHWS [18, 19]. These instruments provide two summary scores: the mental component summary (MCS) and the physical component summary (PCS). The MCS includes questions related to role limitations caused by emotional problems, vitality, social functioning, and mental health. The PCS includes questions related to physical functioning, bodily pain, and general physical health. Higher scores represent better HRQoL. The Short Form-6 Dimension health utility score (SF-6D), which was calculated from the SF-12v2/SF-36v2, is a preference-based measure of HRQoL (i.e., health utility score approximately ranging from 0 to 1) [20, 21]. Again, higher score represents better HRQoL.

**Psychological Complaints**

NHWS respondents reported if they had experienced anxiety, depression, and sleep problems in the past 12 months.

**Work Productivity and Activity Impairment**

Labor force participation was measured by self-reported employment status. Respondents were considered to be in the labor force if employed full-time, part-time, self-employed, or unemployed but looking for work; all others were considered not to be in the labor force (retired, disabled, not employed, and not looking for work, etc.). Work productivity impairment during the past seven days was assessed using the General Health version of the Work Productivity and Activity Impairment questionnaire (WPAI-GH) [22]. This instrument measures absenteeism (the percentage of work time missed because of health), presenteeism (the percentage of impairment experienced while at work because of one’s health), and overall work productivity loss (an overall impairment estimate combining absenteeism and presenteeism), among employed respondents. Activity impairment (the percentage of impairment in daily
activities because of health) was assessed in the full sample of participants.

**Healthcare Resource Use**

Healthcare resource use was defined by the number of visits to different medical providers during the prior six months due to any cause, including visits to physicians and other healthcare professionals, use of the emergency room (ER) and hospitalizations.

**Statistical Analyses**

Prevalence estimates of CU were based on the proportion of the adult population who (1) reported ever experiencing this condition, (2) reported having received a physician diagnosis, and (3) were currently being treated for this condition, by applying weights based on age (18–29, 30–39, 40–49, 50–64, and 65+ years) and gender figures from 2012 (https://www.census.gov/population/international/).

To assess the impact of CU on individuals, respondents who were currently treated for this condition were matched 1:4 with those who reported never experiencing CU on year of survey, age (±2 years), sex, possession of private health insurance, and socioeconomic status. This was followed by regression analyses using generalized linear models, with race (white vs. non-white), household income (above median, below median, or decline to answer), smoking (current, former, or never), obesity, and CCI score (continuous variable) used as covariates. Variables that were measured, but did not differ across groups, were not included as covariates. The HRQoL outcomes were modeled using the normal distribution and identity link function. Binary outcomes were modeled using logistic regression. All other outcomes were modeled using a negative binomial distribution and log-link function.

**RESULTS**

**Prevalence**

For the overall sample (n = 36,000), 320 reported having ever experienced CU, 249 reported having ever been diagnosed with CU, and 127 respondents reported current treatment for this condition. This corresponds to an estimated point prevalence of 0.53, 0.41 and 0.21%, respectively. CU was also found to be more common among women than men. Prevalence was lowest among the elderly (65+ years) and highest in the 45- to 54-year age group (Tables 1, 2).

**Comparison of CU with Controls**

Of the 36,000 total respondents, 127 reported current treatment for CU and 508 matched controls were included in the analyses. Most personal characteristics did not differ across the matched groups, but the mean CCI score was notably more elevated among CU (p < 0.001), indicating that these participants reported a greater comorbidity burden than controls. Smoking status also significantly differed between groups (p = 0.015), as the CU respondents were more likely to be current smokers than controls. There was a non-significant trend for the CU group to more often report being of white race/ethnicity than controls (p = 0.093) (Table 3).

**HRQoL**

In the bivariate analyses for matched comparisons, CU respondents had notably lower MCS, PCS, and SF-6D health utility scores (all p < 0.001) (Fig. 1). In the regression analyses, after adjustment, decrements associated with CU were 5 points for MCS, 2.5 points for PCS, and 0.06 points for SF-6D (all p < 0.01), confirming that CU negatively impacts HRQoL.

**Psychological Complaints**

In the bivariate analyses for matched comparisons, rates of anxiety, depression, and sleep difficulties were almost double the rate for CU respondents compared with controls (all p < 0.001 (Table 4). In the regression analyses, after adjusting for race/ethnicity, comorbidities, and smoking, CU was associated with more than twice the adjusted odds of experiencing anxiety and sleep difficulties (both p < 0.001). However, the increased odds of experiencing...
depression for CU no longer reached significance ($p = 0.060$).

**Work Productivity and Activity Impairment**
In the bivariate analyses for matched comparisons, employed CU respondents reported higher presenteeism and overall work impairment scores, compared with controls (both $p < 0.001$) (Table 5). Similarly, activity impairment was also significantly higher among CU relative to controls ($p < 0.001$). The regression analyses showed CU was associated with 1.5–1.6 times the work and activity impairment of controls, after adjusting for potential confounders (all $p < 0.01$).

**Healthcare Resource Use**
In the bivariate analyses for matched comparisons, much more frequent healthcare resource use was reported among those with CU than controls (Table 6). Specifically, the total number of healthcare provider visits in the previous six months for CU respondents averaged approximately 2.4 times that of controls ($p < 0.001$). In the regression analyses, after adjustment, CU was associated with twice the number of total healthcare provider visits, eight times the number of allergist visits, and twice the number of ER visits compared with controls (all $p < 0.01$).

**DISCUSSION**

The results of the current study showed that, in Brazil, adults with CU have substantially worse outcomes than people living without CU, including HRQoL decrements, anxiety, and sleep difficulties. CU was also associated with significant impairments on work and non-work activities and greatly elevated healthcare resource use.

The prevalence of diagnosed CU among adults in Brazil in this study was similar to what has been reported in prior studies in the US and Europe. However, the prevalence of treated CU

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**Table 1** Prevalence estimate of CU in all Brazilian adults and by gender

| Variables          | Prevalence estimate (95% CI) |          |          |
|--------------------|-----------------------------|----------|----------|
|                    | Overall (%) | Men (%) | Women (%) |
| Ever experienced   | 0.53 (0.44–0.62) | 0.41 (0.29–0.53) | 0.64 (0.52–0.77) |
| Ever diagnosed     | 0.41 (0.33–0.49) | 0.32 (0.21–0.43) | 0.50 (0.39–0.61) |
| Currently treated  | 0.21 (0.15–0.27) | 0.16 (0.08–0.25) | 0.25 (0.15–0.34) |

CI confidence interval, CU chronic urticaria

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**Table 2** Prevalence estimate of CU in all Brazilian adults by age groups

| Age (years) | Currently treated  |          |          | Ever diagnosed  |          |          | Ever experienced |          |          |
|-------------|-------------------|----------|----------|-----------------|----------|----------|------------------|----------|----------|
|             | %                  | 95% LCL  | 95% UCL  | %               | 95% LCL  | 95% UCL  | %                | 95% LCL  | 95% UCL  |
| 18–24       | 0.17               | 0.09     | 0.25     | 0.27             | 0.16     | 0.37     | 0.32             | 0.21     | 0.43     |
| 25–34       | 0.18               | 0.12     | 0.24     | 0.43             | 0.28     | 0.57     | 0.59             | 0.43     | 0.75     |
| 35–44       | 0.31               | 0.12     | 0.51     | 0.53             | 0.32     | 0.74     | 0.64             | 0.42     | 0.87     |
| 45–54       | 0.31               | 0.08     | 0.55     | 0.61             | 0.35     | 0.88     | 0.74             | 0.46     | 1.02     |
| 55–64       | 0.12               | 0.04     | 0.21     | 0.32             | 0.15     | 0.48     | 0.53             | 0.28     | 0.77     |
| 65 and older| 0.03               | 0.00     | 0.06     | 0.10             | 0.00     | 0.25     | 0.11             | 0.00     | 0.25     |

LCL lower confidence limit, UCL upper confidence limit, CU chronic urticaria
in this study was somewhat lower than what has been reported in the US and Europe. In particular, estimates have ranged from 0.5 to 1.0% in US and European adult populations [4–6]. Despite these very modest differences in prevalence estimates, the results of the current study support findings from similar research conducted with participants in other geographies.

With respect to HRQoL and healthcare resource use, the current study found lower HRQoL scores and greater healthcare resource use for those with CU than for controls. Similar associations were found among adults in the US and five European nations [5, 6]. Nevertheless, it is possible that HRQoL and other outcomes may be different among patients with CU in Brazil, relative to those in the US or Europe, given the substantial differences in socioeconomic status between populations in developing nations.

### Table 3

| Patient characteristics in controls and CU respondents after matching | Controls (n = 508) | CU (n = 127) | p value |
|---|---|---|---|
| n/ | %/ | n/ | %/ |
| Age, years (Mean, SD) | | | | 0.982 |
| 37.1 | 11.7 | 37.1 | 11.8 |
| Female | 328 | 64.6% | 82 | 64.6% | 1.000 |
| White | 345 | 67.9% | 96 | 75.6% | 0.093 |
| Employed | 381 | 75.0% | 97 | 76.4% | 0.748 |
| Married/living w/partner | 286 | 56.3% | 76 | 59.8% | 0.471 |
| Completed university | 262 | 51.6% | 60 | 47.2% | 0.383 |
| Socioeconomic status | | | | 0.999 |
| A1/2 | 102 | 20.1% | 26 | 20.5% |
| B1 | 180 | 35.4% | 45 | 35.4% |
| B2 | 157 | 30.9% | 39 | 30.7% |
| C1 | 62 | 12.2% | 15 | 11.8% |
| C2-E | 7 | 1.4% | 2 | 1.6% |
| Private health insurance | | | | 0.186 |
| Median split, reported household income | Lower income | 154 | 30.3% | 30 | 23.6% |
| Higher income | 303 | 59.6% | 87 | 68.5% |
| Decline to answer | 51 | 10.0% | 10 | 7.9% |
| CCI (Mean, SD) | 0.31 | 0.74 | 1.43 | 3.51 | <0.001 |
| BMI categories | | | | 0.122 |
| Underweight | 13 | 2.6% | 7 | 5.5% |
| Normal | 252 | 49.6% | 49 | 38.6% |

#### Table 3 continued

| Controls (n = 508) | CU (n = 127) | p value |
|---|---|---|
| n/ | %/ | n/ | %/ |
| Overweight | 142 | 28.0% | 42 | 33.1% |
| Obese | 94 | 18.5% | 28 | 22.0% |
| Decline to answer | 7 | 1.4% | 1 | 0.8% |
| Smoking status | | | | 0.015 |
| Current | 84 | 16.5% | 35 | 27.6% |
| Former | 116 | 22.8% | 28 | 22.0% |
| Never | 308 | 60.6% | 64 | 50.4% |
| Alcohol use | | | | 0.175 |
| Daily | 13 | 2.6% | 3 | 2.4% |
| Less than daily | 311 | 61.2% | 89 | 70.1% |
| None | 184 | 36.2% | 35 | 27.6% |
| Exercises | 329 | 64.8% | 84 | 66.1% | 0.771 |

BMI body mass index, CCI Charlson comorbidity index, CU chronic urticaria, SD standard deviation
compared with wealthier, developed nations. Generally supporting this idea, prior research has shown that adults with lower socioeconomic status report more severe health impairments, poorer HRQoL, and lower life expectancy than those with higher socioeconomic status [23, 24]. Future research will need to verify this possibility empirically using appropriate cross-national comparisons. Differences in HRQoL exceeded minimally important differences for MCS and SF-6D score thresholds [19, 25, 26]. In the current study, CU respondents also had higher odds of experiencing anxiety and sleep difficulties than controls, which was consistent with previous research [5, 6]. Additionally, CU has been associated with significantly greater odds of any physician visit, an ER visit, or a hospitalization [5], which are in agreement with results from the present study.

Likewise, impairment to work productivity and daily activities in this study were generally aligned with findings from recent international studies. Among respondents from the US, Europe, and Canada, overall work productivity impairment (measured with the WPAI) for those with CU was found to be 26.9% and activity impairment was reported at 32.8% [27]. Adults in Italy with CU were found to have overall work productivity impairment of 22.4% [28]. Collectively, a high degree of overall work productivity loss has implications for indirect costs, which were found in a previous study to range from US$544.80 (France) to US$1287.40 (Germany) per month [29]. This suggests the indirect costs of CU will also be sizeable in Brazil, although this would need to be confirmed with a future study. Therefore, better awareness and greater patient-physician discussion are needed to help reduce this burden on society.
Findings were also consistent with the limited available prior research from Brazil. For example, one study, which was conducted at an outpatient clinic in Sao Paulo, indicated that respondents with CU reported via the Dermatology Life Quality Index (DLQI) a negative impact on their ability to participate in daily and leisure activities, as well as experiencing uncomfortable symptoms (e.g., itching) and feelings of embarrassment from their condition [30]. Another study conducted in a Sao Paulo outpatient clinic assessed HRQoL using the SF-36 domain scores and the DLQI [31]. Although the aforementioned study was mainly concerned with comparing HRQoL among different types of CU, regardless of type, CU was associated with significant impairment in work activities, daily activities, and high levels of fatigue [31]. This prior finding, along with our current findings, highlight the need for patients’ HRQoL to be taken into account in devising strategies to better manage this condition.

**Limitations**

Overall, the findings should be considered in light of the limitations of the methodology. The NHWS may be less representative of the general population in Brazil with respect to

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Table 5  Work and activity impairment among CU respondents relative to controls

| Matched comparisons | Controls \((n = 508)\) Mean (SD) | CU \((n = 127)\) Mean (SD) | \(p\) value | Regression estimates for CU relative to controls |
|---------------------|-------------------------------|----------------------------|-------------|-----------------------------------------------|
| Absenteeism (%) \((ns = 360; 95)\) | 7.9 (19.1) | 7.6 (12.0) | 0.879 | 0.89 (0.50–1.58) \(0.697\) |
| Presenteeism (%) \((ns = 362; 96)\) | 20.2 (27.0) | 36 (29.0) | \(<0.001\) | 1.61 (1.20–2.17) \(0.002\) |
| Overall work impairment (%) \((ns = 360; 95)\) | 24.1 (30.8) | 38.9 (29.2) | \(<0.001\) | 1.51 (1.14–2.01) \(0.005\) |
| Activity impairment (%) \((ns = 508; 127)\) | 23.1 (27.4) | 40.6 (31.2) | \(<0.001\) | 1.5 (1.19–1.88) \(0.001\) |

CI confidence interval, CU chronic urticaria, RR rate ratio, SD standard deviation

Table 6  Higher numbers of health care visits among CU respondents relative to controls

| Matched comparisons | Controls, \((n = 508)\) Mean (SD) | CU, \((n = 127)\) Mean (SD) | \(p\) value | Regression estimates for CU relative to controls |
|---------------------|-------------------------------|----------------------------|-------------|-----------------------------------------------|
| Total HCP visits | 5.2 (7.9) | 12.3 (13.1) | \(<0.001\) | 1.95 (1.51–2.51) \(<0.001\) |
| GP visits | 1.0 (2.5) | 1.4 (2.5) | 0.098 | 1.48 (1.00–2.18) \(0.050\) |
| Allergist visits | 0.1 (0.4) | 0.9 (1.8) | \(<0.001\) | 8.02 (4.64–13.86) \(<0.001\) |
| Psychiatrist visits | 0.2 (0.9) | 0.6 (1.8) | 0.022 | 1.89 (0.89–4.02) \(0.097\) |
| Psychologist/psychotherapist visits | 0.6 (3.3) | 1.7 (5.6) | 0.033 | 1.84 (0.63–5.35) \(0.264\) |
| ER visits | 0.6 (1.4) | 1.8 (4.6) | 0.005 | 2.11 (1.34–3.31) \(0.001\) |
| Hospitalizations | 0.2 (0.7) | 0.5 (1.2) | 0.013 | 1.57 (0.87–2.84) \(0.138\) |

CI confidence interval, CU chronic urticaria, ER emergency room, GP general practitioner, HCP healthcare provider, RR rate ratio, SD standard deviation
socioeconomic status, as the survey tends to overrepresent higher-income insured respondents. This may have a greater impact in Brazil than in some other countries, as private supplemental insurance is provided as a benefit to employees, allowing greater access to care. Another limitation is that the analyses focused primarily on those currently treated with a prescription for CU, which may have excluded some respondents who are currently experiencing hives but not receiving treatment for a variety of different reasons, such as a lack of access to allergy/dermatological care. This may have resulted in an underestimate of the prevalence of CU. The type of urticaria was not available at the time of data collection. Also, in the current study, CU was used as a proxy indicator of CSU. This approach is consistent with prior research using the NHWS [5, 6, 15] and justifiable given that over two-thirds of CU cases can be categorized as CSU cases [3]. Nevertheless, future research should aim to distinguish between the different types of urticaria. The survey is cross-sectional, and thus results do not indicate causal relationships or represent potential changes in these relationships over time.

CONCLUSIONS

The current study provides important new information about the point prevalence of CU in Brazil. The treated estimated prevalence appears somewhat lower than in studies of European and US adults. The current study also characterizes the psychological, physical, and economic costs of CU for patients living in Brazil. Many patients using prescription treatment still experience anxiety and sleep disturbances, poorer HRQoL, significant work and activity impairment, and heavy use of various healthcare resources. Thus, results substantiated the unmet need for better management of this condition in Brazil.

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Disclosures. Maria-Magdalena Balp is an employee of Novartis Pharma AG, Switzerland. Nilcêia Lopes da Silva is an employee of Novartis Biociências S.A., São Paulo, Brazil. Haijun Tian is an employee of Novartis Pharmaceutical Corporation, USA. At the time this study was conducted, Jeffrey Vietri was employed by Kantar Health, which received funding from Novartis Pharma AG and Genentech for conducting the analysis and reporting on this study. Luis Felipe Ensina is a speaker and advisor for Novartis.

Compliance with Ethics Guidelines. All procedures performed in studies involving human participants were in accordance with the ethical standards of the Essex Institutional Review Board (Lebanon, NJ, USA), and the Pearl Institutional Review Board (Indianapolis, IN, USA) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available due to the proprietary nature of the NHWS database, but are available from the corresponding author on reasonable request.
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