

The Relationship Between the Prevalence of Nighttime Gastroesophageal Reflux Disease and Disease Severity

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Abstract

Background Nighttime gastrointestinal reflux disease (GERD) prevalence and severity estimates vary substantially across studies.

Methods We assessed nighttime GERD (NTG) prevalence and symptom frequency and severity through a web survey of US adults, using the GERD Symptom and Medication Questionnaire (GERD-SMQ), a validated symptom questionnaire. NTG was based on episodes of nighttime heartburn per week and time of occurrence. Symptom severity and impact were assessed and compared for GERD cases with and without NTG.

Results GERD prevalence among respondents ($n = 2,603$) was 27%. Forty-five percent of symptomatic GERD respondents had NTG. Among respondents with both

daytime and nighttime symptoms, 51% reported that nighttime symptoms were more bothersome. NTG respondents reported greater disease severity compared with those without ($P < 0.0001$).

Conclusions NTG symptoms are very common among those identified with GERD. People with nighttime symptoms have greater disease severity than those with exclusively or primarily daytime symptoms.

Keywords Gastroesophageal reflux disease · GERD · Nighttime GERD · Prevalence

Introduction

Gastroesophageal reflux disease (GERD) is a chronic disease characterized principally by symptoms of heartburn and acid regurgitation. Up to 44% of the adult population in the US reports symptoms of heartburn and acid regurgitation at least once a month [1], 20% once a week [2], and 7% daily [3]. However, symptoms sufficiently frequent and/or severe enough to impair the individual's health-related quality of life (HRQOL) are not as common. Nighttime reflux episodes occur less frequently, but tend to last longer and result in more severe complications than daytime reflux episodes [4, 5].

The most widely cited estimates of nighttime GERD (NTG) come from two independent nationwide telephone surveys published by Shaker et al. and Farup et al. [6, 7], who found that between 74 and 79% of adults with frequent *heartburn* (at least once weekly) reported experiencing nighttime heartburn during the previous 3 months. While up to 79% of individuals with frequent daytime GERD symptoms reported nighttime symptoms of heartburn or regurgitation [6, 7], it was not clear whether these

Dr. Dean had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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symptoms were frequent and/or severe enough to cause lifestyle impairment.

Although considerable information exists about the prevalence of GERD in general, specific data on the prevalence of nighttime symptoms are less common. In part, this may be due to the lack of clear, uniform diagnostic criteria for NTG [8, 9], which impacts the diagnosis and estimation of NTG prevalence and may result in an over- or under-appreciation of its clinical importance.

Using an Internet-based survey, we evaluated nighttime heartburn and acid regurgitation among respondents, using a validated screening method that takes into account not only the frequency but also the severity of GERD symptoms. Our primary objective was to provide estimates of NTG prevalence and severity among a solicited general population of US adults and to describe the relationship between NTG symptoms and disease severity.

Methods

Study Design

This was a cross-sectional study incorporating an Internet-based survey. An advisory panel of physicians and researchers in gastroenterology and sleep disorders was involved in initial study discussions, the development of the survey instrument, the discussion of the analysis plan, and interpretation of the resulting data; and also the writing of the manuscript.

Data Source and Subjects

Study respondents were adults aged 18 years or older living in the US who were recruited during September 2005. This survey was conducted by the Harris Interactive Service Bureau through their online registration panel Harris Poll Online (HPO). Study participants originally had been recruited for HPO panels through telephone, postal mail, electronic mail, and Internet advertisements, and were willing to answer a questionnaire. Participants were compensated for completing this survey in the form of points redeemable for prizes equivalent to less than \$5. A sample of HPO panel members with a selected demographic profile intended to match that of the US general population received invitations to this study. Respondents had to have initiated the web-based survey and successfully completed the entire questionnaire in order to be included in the analysis.

The study protocol was reviewed by the Western Institutional Review Board (Olympia, WA) and was granted a waiver from full IRB review.

Survey Instrument

The 15-minute online survey included an assessment of GERD symptom frequency and severity using the GERD Symptom and Medication Questionnaire (GERD-SMQ) [10]. This instrument is a validated screening tool designed to assess the frequency and severity of heartburn and acid regurgitation and to adjust GERD status for medication use. The instrument includes six questions pertaining to the presence, frequency, and severity of heartburn and regurgitation, and one question pertaining to the use of over-the-counter and prescription gastrointestinal medication use. Scores range from 0 to 44, with scores greater than 9 indicating the presence of GERD.

Additional investigator-developed questions assessed the average frequency and severity of heartburn and acid regurgitation during the previous 3 months. Frequency was assessed on a scale ranging from ‘none of the time’ to ‘7 days/nights per week.’ Severity was assessed on a 10-point Likert scale ranging from ‘1—very mild’ to ‘10—very severe.’ The frequency and severity of daytime and NTG symptoms were assessed separately. Nighttime symptoms were defined as being at night: (1) while sleeping; (2) while attempting to sleep; or (3) when awakened from sleep. This definition of nighttime was provided throughout the survey wherever nighttime symptoms were assessed.

Study Participants

Among the respondents, we identified those GERD cases who reported experiencing symptoms within the previous 3 months. Symptomatic GERD cases were GERD cases who satisfied GERD-SMQ criteria for GERD during the previous year (GERD-SMQ score >9) and reported experiencing heartburn and/or acid regurgitation within the previous 3 months.

Symptomatic GERD cases were further classified into those with and without NTG. We explored various definitions of NTG, including: (1) having nighttime symptoms only; (2) having *any* nighttime symptoms with or without daytime symptoms; and (3) a minimum frequency of nighttime symptoms. Ultimately, we defined NTG cases as study participants with GERD who also satisfied the following criteria: (a) one or more nights per week with nighttime symptoms in those with only nighttime symptoms or (b) two or more nights per week with nighttime symptoms in those reporting both daytime and nighttime symptoms. Cases without NTG were defined as study participants with GERD who did not satisfy NTG criteria, and included: (a) those with only daytime symptoms of GERD and (b) those having both daytime and nighttime symptoms but <2

nights of symptoms per week (i.e., infrequent nighttime symptoms).

Data Management and Statistical Analyses

Statistical analyses were performed using the SAS statistical package (SAS Version 8.2; SAS Institute, Cary, NC).

The study responders' sociodemographic distribution (by age, gender, race, and income) was compared with: (a) the general population distributions [11] and (b) the distributions of the cohort invited to participate. Study responders can be compared to the invited cohort and the US population to determine how well the final sample reflects the distributions in the underlying population from which it was drawn. Participants with and without NTG were also compared on the distributions of selected demographics. Differences in means were evaluated using the *t*-test procedure, and differences in proportions were evaluated using chi-square tests. *P*-values were reported.

Among symptomatic GERD cases, the number of nights with symptoms and the impact of daytime and nighttime symptoms were obtained. GERD cases reported whether nighttime symptoms were more bothersome, daytime symptoms were more bothersome, or daytime and nighttime symptoms were equally bothersome. Among NTG cases, severity classification was based on the highest value from among the nighttime heartburn and nighttime acid regurgitation severity measures, each assessed on a 10-point Likert scale. Severity was then categorized as mild (1–4), moderate (5–7), or severe (8–10). For cases without NTG, severity was classified in the same manner based on the highest value from daytime heartburn and daytime acid regurgitation severity scores. The difference in severity score distribution between the groups with and without NTG was evaluated using the chi-square test. The difference in the mean proportions across bothersomeness of symptoms by NTG status was also assessed using the chi-square test. *P*-values were reported.

The association between NTG status and GERD severity score was measured by odds ratios. Moderate and severe GERD groups were compared to the mild group (i.e., reference group). The 95% confidence intervals (CIs) were reported.

Results

Of 18,213 HPO members invited to participate in the survey, 2,805 (15%) initiated the survey screener during the 3-week fielding period and 2,603 satisfied the study criteria and completed the questionnaire. Invited participants were sampled from HPO members in an attempt to reflect general sociodemographic distributions. Compared to the

general US population, the sociodemographics of the invited participants (i.e., online sample) were similarly distributed across gender and income categories but were undersampled within the older age groups and were more likely to be white (Table 1). Compared with the sociodemographic distributions of the online sample, those who completed the questionnaire (i.e., respondents) were slightly more likely to be female (56 vs. 52%) and more likely to be white (86.8 vs. 78.8%). Similarly, compared with the US population distributions, respondents were more likely to be female (56 vs. 52%) and white (87 vs. 67%).

A comparison between symptomatic respondents with and without NTG suggested that these groups were similar in their sociodemographic distributions except that respondents with NTG were less likely to be white ($P = 0.04$; Table 2). Respondents with and without NTG also did not differ in their treatment patterns for over-the-counter or prescription medications ($P = 0.9996$ and $P = 0.9998$ for over-the-counter and prescription medications, respectively). Over three-quarters of those with heartburn were taking over-the-counter medication at least four times per week (79 vs. 74% for daytime and nighttime heartburn, respectively). Similarly, 81 and 77% of those suffering daytime and nighttime symptoms, respectively, reported taking prescription medication at least four times per week.

Symptoms of GERD were common in the study respondents. Among all 2,603 respondents, 42.1% reported experiencing heartburn at any time during the previous 12 months, and 45.5% reported acid regurgitation. However, not all of the respondents reporting symptoms met the criteria required for GERD. Based on scores obtained from the GERD-SMQ, the prevalence of GERD in this sample was 26.9% ($n = 701$). Among these GERD-SMQ cases, more than 95% ($n = 668$) were symptomatic (i.e., they reported experiencing symptoms within the previous 3 months).

The Prevalence of NTG

Daytime and nighttime symptoms of heartburn and acid regurgitation during the previous 3 months were explored among symptomatic GERD cases. Slightly more than 9% of GERD cases reported only daytime symptoms, while 7.6% reported only nighttime symptoms (Table 3). The majority of GERD cases (83.2%) reported both daytime and nighttime symptoms.

Thus, if NTG were defined as having nighttime symptoms only, then as few as 7.6% of GERD cases would be classified as NTG (Table 3). On the other hand, if NTG were defined as having *any* nighttime symptoms with or without daytime symptoms, then the proportion of GERD cases with NTG would be as high as 91%, and the overall

Table 1 Sociodemographic comparison among respondents versus general population

	Respondents (<i>n</i> = 2,603) <i>n</i> (%)	Online sample ^b (<i>n</i> = 18,213) <i>n</i> (%)	General US population [11] %
Gender			
Male	1,159 (44.5)	8,749 (48.0)	48.2
Female	1,444 (55.5)	9,464 (52.0)	51.8
Age by category ^a			
18–29	493 (18.9)	4,036 (22.3)	21.2
30–39	520 (20.0)	3,845 (21.3)	19.1
40–49	538 (20.7)	3,756 (20.8)	21.0
50–59	475 (18.3)	3,745 (20.7)	16.7
60–69	357 (13.7)	1,726 (9.6)	10.5
70+	220 (8.5)	955 (5.3)	11.5
Mean age (years)	46	44	–
Race/ethnicity ^a			
White	2,177 (86.8)	10,373 (78.7)	67.3
Black/African American	51 (2.0)	496 (3.7)	12.0
Asian/Pacific Islander	85 (3.4)	442 (3.3)	4.3
Native American/Alaskan Native	30 (1.2)	223 (1.7)	0.6
Hispanic	102 (4.1)	860 (6.5)	14.2
Other	64 (2.6)	449 (6.1)	1.6
Income ^a			
<\$25,000	607 (28.1)	2,375 (25.1)	28.3
\$25,000–\$49,999	726 (33.6)	3,107 (32.8)	26.7
\$50,000–\$99,999	632 (29.3)	2,806 (29.6)	29.3
\$100,000 or more	195 (9.0)	1,184 (12.4)	15.7

^a Race/ethnicity missing for 94 survey respondents. Income missing for 443 survey respondents

^b *n*-Values estimated based on percentage

prevalence of NTG would be 24.5% of the total population sampled. If NTG were defined as having (a) only nighttime symptoms or (b) at least 2 nights per week with symptoms (among those with daytime and nighttime symptoms), then approximately 45% of GERD cases would have had NTG, and, by this definition, the overall prevalence of NTG would be 12.1% in the population intended to reflect the adult US population.

NTG by GERD Severity Score

GERD cases reporting both daytime and nighttime symptoms were asked about their symptoms (Fig. 1). Approximately 25% reported that daytime symptoms were more bothersome than nighttime symptoms, while more than 51% said that nighttime symptoms were more bothersome. The remaining approximate quartile reported that daytime and nighttime symptoms were equally bothersome.

Those with NTG reported greater disease severity than those without NTG ($P < 0.0001$; Fig. 2). Among NTG cases, 33.0% were categorized as severe compared with fewer than 9% among the cases without NTG. The odds of having moderate GERD symptoms as opposed to mild

were 2.1 times as great among those with NTG compared to those without NTG (odds ratio [OR] = 2.1; 95% CI, 1.4–3.1; Fig. 3). The odds for having severe GERD symptoms as opposed to mild were eightfold greater among those with NTG compared to those without NTG (OR = 8.5; 95% CI, 5.0–14.7).

Discussion

Symptoms of heartburn and acid regurgitation were reported commonly among members of this study population, which was sampled with the intention to reflect the US adult population. Based on findings from the GERD-SMQ, the prevalence of GERD in this large general population sample was 26.9%. Applying a more stringent definition of NTG than that used for previously reported estimates of nighttime symptoms, approximately 45% of the symptomatic GERD sufferers had NTG. The majority of patients with both daytime and nighttime symptoms reported their nighttime symptoms as more bothersome, and patients with NTG also reported greater disease severity than did those without NTG.

Table 2 Sociodemographic comparison among respondents with and without nighttime gastrointestinal reflux disease (NTG)

	With NTG (<i>n</i> = 303) <i>n</i> (%)	Without NTG (<i>n</i> = 365) <i>n</i> (%)	<i>P</i> -value With versus without NTG
Gender			
Male	111 (36.6)	138 (37.8)	0.7546
Female	192 (63.4)	227 (62.2)	
Age by category			
18–29	44 (14.5)	51 (14.0)	0.3822
30–39	62 (20.5)	54 (14.8)	
40–49	82 (27.1)	97 (26.6)	
50–59	60 (19.8)	79 (21.6)	
60–69	36 (11.9)	56 (15.3)	
70+	19 (6.3)	28 (7.7)	
Mean age (years)	46.0	48.1	0.0654
Race/ethnicity ^a			
White	252 (85.7)	328 (91.4)	0.0368
Black/African American	6 (2.1)	5 (1.4)	
Asian/Pacific Islander	8 (2.7)	2 (0.6)	
Native American/Alaskan Native	4 (1.4)	7 (2.0)	
Hispanic	16 (5.4)	7 (2.0)	
Other	8 (2.7)	10 (2.8)	
Income ^a			
<\$24,999	84 (31.7)	82 (25.9)	0.1069
\$25,000–\$49,999	75 (28.3)	113 (35.7)	
\$50,000–\$99,999	77 (29.1)	98 (30.9)	
\$100,000 or more	29 (10.9)	24 (7.6)	

^a Race/ethnicity missing for nine NTG cases and six controls without NTG. Income missing for 38 NTG cases and 48 controls without NTG

Previous research has shown that nighttime heartburn and acid regurgitation may produce a greater burden of illness than similar symptoms that occur primarily during the daytime [6, 7, 12]. However, identifying cases with a truly increased burden of illness from nighttime symptoms can be difficult. It is not clear whether an increased burden of illness is associated with GERD cases reporting only nighttime symptoms, cases where nighttime symptoms are the most severe, or cases where nighttime symptoms are more frequent.

NTG has been assessed in a number of randomized clinical trials. Across these published studies, there are variations in the time window used for the evaluation of nighttime symptoms or pH levels, which are based upon some combination of a specific time frame, sleep, and/or posture. However, in an observational study where the measurements are far less controlled and investigators are far less likely to use daily diaries or monitor pH levels, definitions more applicable to a patient are used.

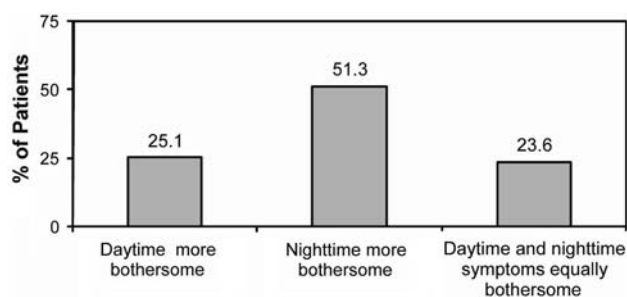
Our study reveals that estimates of the proportion of GERD cases with NTG can vary greatly depending on the criteria used for identification. Although it was evident that GERD cases with nighttime symptoms alone should be classified exclusively as NTG, it was less clear how to

classify the larger subgroup of NTG cases that had both daytime and nighttime symptoms. In our study, only a small proportion of GERD cases reported just daytime or just nighttime symptoms, with the majority (83.2%) reporting both. These results are similar to those reported in two separate national samples, where three-quarters of people suffering from weekly symptoms reported nighttime heartburn and/or acid regurgitation [7]. When more stringent criteria were applied and NTG was defined by a minimum frequency of nights with symptoms, i.e., (a) only nighttime symptoms or (b) at least 2 nights per week with symptoms (among those with daytime and nighttime symptoms), then approximately 45% of GERD cases had NTG. Since requiring at least 2 nights per week with symptoms could inflate findings of severe NTG, an exploratory sensitivity analysis was conducted reclassifying the 71 respondents with only 1 night per week with symptoms as meeting NTG criteria. While the results assessing NTG by GERD severity score were attenuated, the findings did not differ considerably from those reported, suggesting that even those suffering from less frequent nighttime symptoms consider their nighttime symptoms to be more severe.

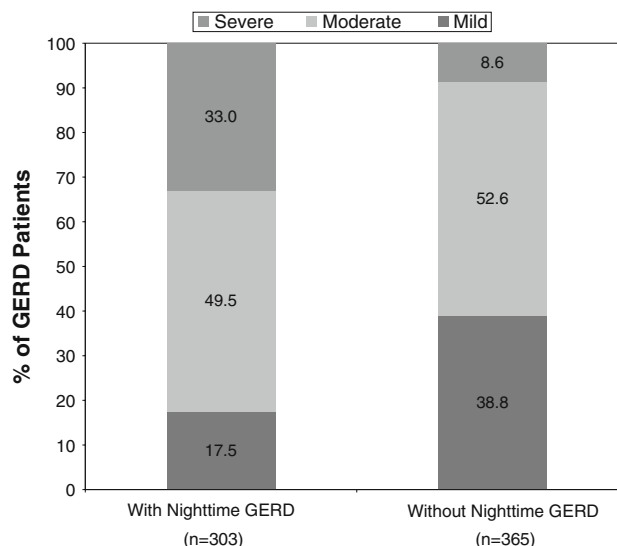
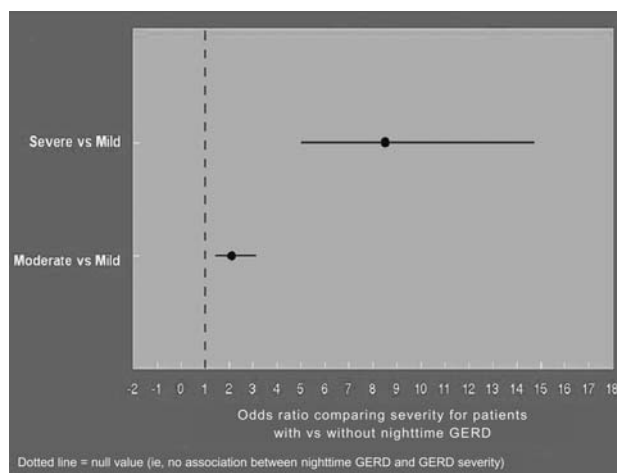
The findings of our study suggest that nighttime symptoms are perceived by patients as more severe than daytime

Table 3 Distribution of symptomatic GERD cases by daytime and nighttime symptom occurrence during the previous 3 months ($n = 668$)

	<i>n</i> (%)
Daytime symptoms of GERD only	61 (9.13)
<1 day per week with symptoms	33 (54.1)
1 day per week with symptoms	12 (19.7)
2 days per week with symptoms	8 (13.1)
3 days per week with symptoms	6 (9.8)
4 days or more per week with symptoms	2 (2.2)
Nighttime symptoms of GERD only	51 (7.6)
<1 night per week with symptoms	34 (66.7)
1 night per week with symptoms	5 (9.8)
2 nights per week with symptoms	5 (9.8)
3 nights per week with symptoms	5 (9.8)
4 nights or more per week with symptoms	2 (4.0)
Both daytime and nighttime symptoms of GERD	556 (83.2)
Both daytime and nighttime symptoms with less than 1 night per week with symptoms	233 (41.9)
Both daytime and nighttime symptoms with 1 night per week with symptoms	71 (12.8)
Both daytime and nighttime symptoms with 2 nights per week with symptoms	77 (13.8)
Both daytime and nighttime symptoms with 3 nights per week with symptoms	69 (12.4)
Both daytime and nighttime symptoms with 4 or more nights per week with symptoms	106 (19.1)
Total	668 (100.0)

**Fig. 1** Daytime versus nighttime symptoms reported as more bothersome among gastrointestinal reflux disease (GERD) cases with both daytime and nighttime symptoms ($n = 556$)

symptoms; thus, GERD cases with NTG were more likely to report severe symptoms compared to those without NTG. The odds of having moderate or severe GERD as opposed to mild GERD were significantly greater among NTG cases compared to those without NTG. In fact, the odds of having severe GERD versus mild GERD were eightfold higher among those with NTG compared to those without NTG. In support of this observation, more than half of those reporting both daytime and nighttime symptoms reported that their nighttime symptoms were more

**Fig. 2** Distribution of patients with and without nighttime GERD (NTG) by severity of GERD symptoms during the previous 3 months. chi-square, $P < 0.0001$ for NTG compared with daytime GERD**Fig. 3** Patients with NTG graded their symptoms as more severe than those without NTG

bothersome than their daytime symptoms. These results could, in part, explain the impaired HRQOL seen in patients with nighttime symptoms that has been reported by others [6, 7].

Possible limitations in the interpretation of our study results should be considered. First, the response rate was lower than expected. However, while population-based studies may reduce the bias associated with sampling in observational studies, our participants were sampled in an effort to reflect the general US population on demographic variables. The composition of invited participants in this study suggests a distribution similar to the general US adult population, despite the lower-than-expected response rate. Second, symptoms were assessed through self-report rather

than physician diagnosis; therefore, recall bias may have affected the assignment of case status. However, symptoms were examined through the assessment of frequency, severity, and medication use—all of which are elements used in the validated algorithm (GERD-SMQ) utilized to assign GERD to cases. Additionally, we have no reason to suspect differential bias among cases with versus cases without NTG. Third, our method for assessing severity was based on the maximum severity reported for either daytime or nighttime heartburn or acid regurgitation in order to assign the highest severity classification to cases. While we explored other methods for assigning symptom severity, we found little variation across classification schemes and we believed that the maximum severity scores would more accurately reflect the overall burden of illness. Fourth, Internet surveys can suffer from shortcomings, including the need to format validated instruments for this media and the need to sample participants in an effort to reflect the demographic and clinical distribution of the base population.

In conclusion, by focusing on the severity of symptoms, this study demonstrates the high prevalence of clinically meaningful NTG in this adult US population. Nighttime symptoms were reported qualitatively as more bothersome than daytime symptoms, and quantitatively rated as more severe, supporting the conclusion that those with nighttime heartburn or acid regurgitation may have more severe GERD than those with primarily daytime symptoms. Knowledge regarding the presentation of patients with nighttime symptoms meeting criteria serious enough to impact their quality of life may aid in the screening, diagnosis, and treatment of individuals at high risk for experiencing more severe GERD.

Statement of Interests

Authors' Declaration of Personal Interests

- (i) Dr. Fass has served as a consultant, speaker, or member of an advisory board, or has received research funding from Wyeth, AstraZeneca, Altana, Takeda, Eisai, Xenoport, Procter & Gamble, Vecta, Addex, and GlaxoSmithKline. Dr. McGuigan has served as a speaker, a consultant, and an advisory board member for Wyeth Pharmaceuticals, and has received research funding from Wyeth Pharmaceuticals. Dr. Johnson has served as a consultant or member of an advisory board, or has received research funding from Wyeth, AstraZeneca, Santarus, and Tap Pharmaceutical Companies. Dr. Orr has served as a consultant or member of an advisory board or speaker's bureau for Wyeth, AstraZeneca, Santarus, and TAP.

- (ii) Dr. Morgenstern is an employee of Wyeth Pharmaceuticals. Dr. Yan was an employee of Wyeth Pharmaceuticals at the time of drafting this manuscript. Messrs. Aguilar and Calimlim and Drs. Dubois and Dean are employees of Cerner LifeSciences, a consulting company that provides services to the pharmaceutical industry.
- (iii) Drs. Morgenstern and Yan own stocks and shares in Wyeth Pharmaceuticals.

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- (ii) The *writing or preparation* of this paper was funded in full by Wyeth Pharmaceuticals.
- (iii) Initial data analyses were undertaken by no one besides the authors, affiliated and funded as stated above.
- (iv) Writing support was provided by no one besides the authors, affiliated and funded as stated above.

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