

# Relationships Among Adverse Events, Disease Characteristics, and Demographics in Treatment of Postherpetic Neuralgia With Gastroretentive Gabapentin

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**Objectives:** To characterize risk factors for occurrence of adverse events (AEs) and treatment discontinuations due to AEs for improving safety and tolerability of treatment of postherpetic neuralgia (PHN).

**Methods:** Patients with PHN ( $n = 556$ ) received 1800 mg once-daily gastroretentive gabapentin (G-GR) in 2 phase 3 and 1 phase 4 study. Safety assessments included the incidence and severity of AEs and analysis of discontinuations due to AEs. Multivariable, logistic regression analyses examined predictors of AE reporting and discontinuations due to AEs.

**Results:** In total, 53.2% of patients reported any AE, and 12.9% discontinued because of AEs. Both AE incidence and treatment discontinuations decreased rapidly during the 2-week titration to sustained, low levels. The probability to report any AE was 0.6 for females versus 0.4 for males, whereas there were no differences in probabilities for age (less than 75 vs. 75 y and older) and race (nonwhite vs. white). Consistent with this, only female sex was a significant ( $P = 0.0006$ ) predictor of AE reporting. Experiencing moderate ( $P \leq 0.0001$ ) or severe ( $P = 0.0006$ ) AEs, but not patient demographics, was predictive of treatment discontinuations. The probability of discontinuation due to moderate AEs was 0.4 and 0.5 for severe AEs.

**Discussion:** The tolerability of G-GR was not affected by patient age, but was affected by AE severity. Although being female was predictive of reporting AEs, it did not influence treatment discontinuation. Given that PHN is a disease for which the risk and duration of PHN increases with age and with being female, G-GR appears to be a well-suited treatment option for PHN.

**Key Words:** postherpetic neuralgia, neuropathic pain, gabapentin, gastroretentive, safety

(*Clin J Pain* 2015;31:983–991)

Received for publication October 6, 2014; revised January 23, 2015; accepted December 20, 2014.

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Supported by Depomed Inc., Newark, CA. I.B. is an employee and shareholder of Depomed Inc. The remaining authors declare no conflict of interest.

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DOI: 10.1097/AJP.0000000000000206

Postherpetic neuralgia (PHN) is a neuropathic pain syndrome that persists for months to years after resolution of the herpes zoster (HZ) rash (shingles).<sup>1</sup> HZ is an infection resulting from reactivation of the varicella-zoster virus that has been dormant for many years after the primary infection (chickenpox).<sup>2</sup> As many as 20% of patients with HZ develop PHN, and the risk, frequency, and severity of PHN increases with advancing age.<sup>3–6</sup> Approximately half of all PHN cases occur in persons older than 60 years,<sup>3–6</sup> and as the population ages,<sup>7</sup> the incidence of PHN is expected to increase. Other major risk factors for developing PHN include decreased cell-mediated varicella-zoster virus immunity, female sex, severity of the acute HZ infection, and the presence of a notable prodrome.<sup>5,8</sup>

A number of factors can complicate the management of PHN and should be considered when prescribing pain medication.<sup>9</sup> Because patients with PHN are older, they often have chronic, comorbid conditions,<sup>10,11</sup> and are at increased risk for polypharmacy.<sup>12</sup> If the pharmacological intervention for PHN requires multiple-dose regimens, this can result in poor compliance with the treatment, further diminishing the quality of PHN management.<sup>13,14</sup> Long and/or complicated titration to therapeutically effective dosages can lead to sub-optimal dosing leaving patients undertreated.<sup>13,15</sup> Furthermore, pathophysiological changes that accompany normal aging can lead to clinically important changes in pharmacodynamics and pharmacokinetics (ie, drug absorption, metabolism, renal elimination, and bioavailability) of drugs.<sup>16</sup> Older adults have also greater potential for experiencing harmful adverse reactions, which may further limit the effectiveness of treatment.<sup>17,18</sup>

To date, no cure for PHN exists, and the effective management of PHN remains an ongoing challenge, with no single, best therapy yet identified.<sup>13</sup> Agents from 4 therapeutic categories are recommended for the management of PHN: tricyclic antidepressants, gabapentinoids, opioids, and topical anesthetics.<sup>19</sup> However, some of them may not be appropriate for older patients. For example, the Beers criteria by the American Geriatrics Society identified tricyclic antidepressants as a class of drugs to avoid in older adults.<sup>20</sup> Also, given the complexity of opioid management, the American Pain Society and American Academy of Pain Medicine have suggested cautious initiation and titration of opioids in frail older persons or those with comorbidities.<sup>21</sup>

Gabapentinoids—immediate-release gabapentin, gastroretentive gabapentin (G-GR), gabapentin enacarbil, and pregabalin—are the only oral medications approved by the Food and Drug Administration (FDA) for the treatment of PHN, and are recommended as first-line therapies.<sup>19,22</sup> Because gabapentinoids are not metabolized by the cytochrome P450 system drug-metabolizing enzymes but are

renally excreted, they have low propensity for drug-drug interactions (daily dosing should be adjusted in patients with reduced renal function). Therefore, gabapentinoids are especially attractive for patients with PHN, who are often taking several concomitant medications. The safety profile is similar among all gabapentinoids, with dizziness and somnolence being the most commonly reported AEs by PHN patients. However, the incidence of AEs varies significantly, with dosage-related rates for dizziness of up to 30% for immediate-release gabapentin and gabapentin enacarbil, and dosage-related rates for daytime somnolence of up to 27% and 14%, respectively.<sup>23–25</sup>

Most gabapentinoids, as well as other PHN treatments, require multiple daily doses and often a long titration to efficacious dosages. G-GR is the only once-daily oral treatment option available.<sup>26</sup> G-GR employs a polymer-based technology that swells when it comes in contact with gastric fluid.<sup>26</sup> When taken with food, the swollen tablet remains in the stomach for 8 to 10 hours and gradually releases gabapentin to its optimal site of absorption in the upper small intestine, allowing less frequent dosing compared with the thrice-daily dosing of the immediate-release gabapentin, as well as a simpler titration regime.

The efficacy and safety of G-GR in the management of PHN has been demonstrated in 2 phase 3, placebo-controlled studies, and 1 phase 4, open-label study.<sup>27–29</sup> Across clinical studies, patients treated with G-GR reported significant reductions from baseline in various measures of pain intensity and quality, and the interference of pain with various aspects impacting patients' quality of life. Overall, nearly half of patients felt "Much" or "Very Much" improved on the Patients' Global Impression of Change. G-GR was generally safe and well tolerated, and discontinuations due to adverse events (AEs) were 9.7% to 18.8% across the studies. In total, 48% of patients in phase 3 and 51% of patients in phase 4 reported any AE, and the most common were dizziness and somnolence (10.9% to 13.7% and 4.5% to 5.6%, respectively).<sup>29,30</sup> Comparisons of efficacy and safety of G-GR between younger and older patient populations in the phase 3 (less than 75 y vs. 75 y and older) and phase 4 (70 y and younger vs. older than 70 y) studies revealed no significant differences between the age groups.<sup>29,31</sup>

Although data on the safety of all gabapentinoids, including G-GR, is readily available, results from exploratory investigations describing relationships among AE occurrence, AE types, discontinuations due to AEs, various disease characteristics, and patient demographics are lacking. Better understanding of the safety and tolerability profile as well as risk factors that lead to AE reporting and study discontinuations can lead to better treatment design and monitoring, which is especially important for the vulnerable PHN population where AEs can limit the effectiveness of the treatment. To address these issues, we performed comprehensive analyses in a large patient population from integrated phase 3 and 4 programs for the treatment of PHN with G-GR.

## METHODS

### Patients

Data from patients treated with G-GR in 2 phase 3, double-blind, randomized, placebo-controlled studies and 1 phase 4, open-label, single-arm study were integrated before this analysis. Details of the 3 individual studies have been

previously described.<sup>27–29</sup> Study protocols were approved by the appropriate institutional review boards/ethics committees at each center, and were conducted in accordance with International Conference on Harmonization Good Clinical Practices guidelines. Written informed consent was obtained from each patient before enrollment in the study.

Main patient inclusion criteria in the 2 phase 3 studies were 18 years and older of age with neuropathic pain for  $\geq 3$  months (in the first study) or  $\geq 6$  months (in the second study) after the healing of HZ skin rash; an average daily pain score of  $\geq 4$ —based on an 11-point Likert scale (where 0 = no pain and 10 = worst possible pain)—at the end of a 1-week pretreatment baseline period; a washout period for patients being treated with pain medications that could affect the pain score before the baseline week; a negative pregnancy test at screening and randomization for women of child-bearing potential, and the use of an acceptable method of birth control throughout the study. Main exclusion criteria included prior lack of response to treatment with  $\geq 1200$  mg/d gabapentin or  $\geq 300$  mg/d pregabalin; dose-limiting AEs with gabapentin or hypersensitivity to gabapentin; neurolytic/neurosurgical treatment for PHN; severe pain from causes other than PHN; use of injected anesthetics or corticosteroids within 30 days of baseline; immunocompromised state; and creatinine clearance (CrCl)  $< 50$  mL/min. For the phase 4 study, patients were relatively unselected to reflect the real-world population—inclusion criteria were 18 years and older with active PHN, regardless of their baseline pain scores, and exclusion criteria were limited to those in the product label (pregnant women or nursing mothers, patients with hypersensitivity to gabapentin, and patients who had an estimated CrCl  $< 30$  mL/min or were on hemodialysis). There were no restrictions on the use of prior medications in the phase 4 study, and the use of concomitant neuropathic pain medication was permitted and documented.

### Treatments and Procedures

All 3 studies shared a similar G-GR treatment schedule, which included a 2-week titration period, a stable-dose treatment period (8 wk for phase 3 and 6 wk for phase 4), and a 1-week dose tapering period. The 2-week titration period used a set schedule: day 1: 300 mg; day 2: 600 mg; days 3 to 6: 900 mg; days 7 to 10: 1200 mg; days 11 to 14: 1500 mg; day 15: 1800 mg. During the stable-dose treatment period, patients received 1800 mg G-GR once-daily with the evening meal. The schedule for 1-week dose tapering was  $2 \times 600$  mg for 3 days and  $1 \times 600$  mg for the last 4 days. The end of study in the current, integrated analysis is therefore week 10 for the phase 3 studies and week 8 for the phase 4 study. In the phase 3 studies, AEs were collected through week 12 and for the phase 4 study, AEs were collected through week 9; therefore, the current integrated analysis includes common data through week 9.

### Safety Evaluations

Patients who took  $\geq 1$  dose of study medication were included in the current safety analysis (placebo groups from phase 3 studies were not included; there was no placebo group in the phase 4 study). Safety assessments included the incidence and severity of AEs and serious AEs, analysis of discontinuations due to AEs, clinical laboratory assessments of serum chemistry and hematology, vital signs, and findings of physical examination. Severity of AEs are defined as mild (the event may be noticeable to the patient,

but does not influence the patient’s daily activities; it usually does not require special treatment), moderate (the event may result in slight discomfort for the patient, and performance of the patient’s daily activities may be influenced; it may require intervention), or severe (the event may result in severe discomfort for the patient and usually interferes with the patient’s daily activities; the patient may not be able to continue in the study; treatment or other intervention is usually needed). All AEs were linked to System Organ Class and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities coding (MedDRA; Version 9.0 in phase 3 and Version 14.0 in phase 4).

**Statistical Methods**

Patients with >1 PT within a System Organ Class were counted only once. Patients with >1 occurrence of the same PT were counted only once within that term and at the highest severity grade. To determine probabilities for AE occurrence or discontinuations due to AEs, univariable, logistic regression analyses were performed. To determine predictive factors for AE occurrence or discontinuations due to AEs, multivariable, logistic regression analyses were performed. Three regression analyses were performed to identify predictors of reporting

AEs: (1) at any time during the study; (2) at week 1-2 (titration); (3) and after week 2; and 2 models were used (Table 1). Model 1 included patient demographics (age, sex, and race) as independent variables. Model 2 included additional independent variables: the Visual Analog Scale (VAS) and Brief Pain Inventory (BPI) scores at baseline; BPI and VAS scores at week 2 were additionally used for the analysis of AE reporting after week 2. VAS measures pain intensity on the 100-mm scale, and the BPI measures the severity of pain and the impact of pain on daily functions on a 0 to 10 numerical rating scale (where 0 = no pain/interference; 10 = worst imaginable pain/interference). The 3 types of pain severity on the BPI are Worst pain, Least pain, and Average pain, and the 7 types of interference include General activity, Mood, Walking ability, Normal work, Relationship, Sleep, and Enjoyment of life; there is also an Average of interference scores.

Because of the small number of patients, regression analyses for discontinuations due to AEs were performed only for discontinuations at any time (Table 1). Model 1 included patient demographics (age, sex, and race) as independent variables. Additional independent variables in model 2 were AE severity (mild, moderate, or severe), most common AEs (occurring in ≥2% of patients), and the VAS and BPI scores at baseline. A P-value of ≤ 0.05 was considered statistically significant.

**TABLE 1.** Models for Regression Analysis to Identify Predictive Factors

Time Periods	Independent Variables
<b>AE reporting</b>	
Model 1	
Any time	Patient demographics: age (< 75 vs. ≥ 75 y), sex (female vs. male), and race (nonwhite vs. white)
Week 1-2	
After week 2	
Model 2	
Any time	Patient demographics: age (< 75 vs. ≥ 75 y), sex (female vs. male), and race (nonwhite vs. white) Baseline VAS Baseline BPI
Week 1-2	Patient demographics: age (< 75 vs. ≥ 75 y), sex (female vs. male), and race (nonwhite vs. white) Baseline VAS Baseline BPI
After week 2	Patient demographics: age (< 75 vs. ≥ 75 y), sex (female vs. male), and race (nonwhite vs. white) Baseline VAS Baseline BPI VAS at week 2 BPI at week 2
<b>Discontinuations due to AEs (any time)</b>	
Model 1	
	Patient demographics: age (< 75 vs. ≥ 75 y), sex (female vs. male), and race (nonwhite vs. white)
Model 2	
	Patient demographics: age (< 75 vs. ≥ 75 y), sex (female vs. male), and race (nonwhite vs. white) AE severity (mild, moderate, or severe) Most common AEs (occurring in ≥2% of patients) Baseline VAS Baseline BPI

AE indicates adverse event; BPI, Brief Pain Inventory; VAS, Visual Analog Scale.

**RESULTS**

**Patients**

A total of 556 patients treated with once-daily 1800 mg G-GR were included in the safety population for the current analysis (Fig. 1). Almost all patients (91.7%) completed the 2-week titration period (Fig. 1). In total, 21.0% of patients discontinued the study early, and the most common reasons for discontinuation included AEs (12.9%), withdrawal of consent (3.1%), and lack of efficacy (2.5%). The mean age (SD) of all patients was 66.7 years (12.9 y) (range, 18 to 92 y); most patients (84.0%) were older than 55 years of age (Table 2). The majority of patients were female (60.3%) and white (86.2%). The mean (SD) baseline pain intensity measured on the 100-mm VAS was 62.2 (18.8).

**Incidence of AEs**

In total, 53.2% of patients reported ≥ 1 AE, and the most common AEs (occurring in ≥4% of patients) were dizziness (11.9%), somnolence (4.9%), and headache (4.0%) (Table 3). The incidence of all AEs decreased rapidly during the 2-week titration period (week 1, 21.2%; week 2, 12.8%), and this included the most common AEs, dizziness, and somnolence (Fig. 2A). The analysis of the 2-week titration period by day showed that small proportion of patients reported any AE each day (Fig. 2B). The incidence of AE reporting was evenly distributed throughout the period, with only slightly more reports of AEs (including dizziness and somnolence) during days 1 to 5.

Seventy-two (12.9%) patients discontinued the study due to AEs, and the most common AEs (occurring in ≥1% of patients) leading to discontinuation were dizziness (3.6%), somnolence (1.6%), and nausea (1.1%) (Table 3). Forty-two (7.6%) patients discontinued during the 2-week titration period (Table 3), and the majority of these discontinuations (6.5%) took place during the first week of the titration period (Fig. 2C). When the 2-week titration period was analyzed by day, very small proportion of patients discontinued treatment due to an AE each day—approximately 1% of patients

Safety population	556
Completed 2-week titration	510
Completed study	439
Discontinued early	117
Adverse event	72
Lack of efficacy	14
Protocol violation	3
Lost to follow-up	4
Withdrew consent	17
Death	0
Other	7
Discontinued during 2-week titration	55
Adverse event	42
Lack of efficacy	2
Protocol violation	1
Lost to follow-up	0
Withdrew consent	9
Death	0
Other	1

FIGURE 1. Patient disposition.

discontinued each day during the first week of titration, and approximately 0.2% of patients discontinued each day during the second week of titration (Fig. 2D).

The vast majority of AEs were mild or moderate (Fig. 3A). During weeks 1 to 4, most treatment discontinuations were due to moderate AEs (4.1% of patients at week 1 to 0.4% of patients at week 4), whereas after week 4, discontinuations were evenly distributed among patients experiencing mild, moderate, or severe AEs (Fig. 3B). However, when discontinuations were adjusted for AE occurrence, the analysis revealed that most study discontinuations were due to severe AEs—43.3% of patients who reported severe AEs discontinued, whereas 33.3% of patients who reported moderate AEs and 11.7% of patients who reported mild AEs discontinued early (Fig. 3C).

### Risk Factors for AEs

In model 1, significant predictors of AE reporting included sex—females were 1.8 times more likely to report AEs at any time ( $P = 0.0006$ ), 1.8 times more likely at week 1-2 ( $P = 0.0027$ ), and 1.5 times likely ( $P = 0.0397$ ) after week 2 than were males (Table 4). Nonwhite patients were 1.8 times more likely ( $P = 0.0188$ ) to report any AE at week 1-2 than were white patients; race was not a significant factor at any time or after week 2. When adjusted for other covariates in model 2, compared with males, females were 1.9 times more likely to report AEs at any time ( $P = 0.0006$ ), and 1.9 times more likely at week 1-2 ( $P = 0.0015$ ) (Table 5). For occurrence

TABLE 2. Baseline Characteristics

	G-GR 1800 mg/d (n = 556)
Age (y)	
Mean (SD)	66.7 (12.9)
Median	69.0
Minimum-maximum	18.0-92.0
Age category (y) (n [%])	
< 55	89 (16.0)
55-64	109 (19.6)
65-74	195 (35.1)
≥ 75	163 (29.3)
Sex (n [%])	
Male	221 (39.7)
Female	335 (60.3)
Race (n [%])	
White	479 (86.2)
Black or African American	29 (5.2)
Asian	6 (1.1)
Hispanic or Latino	38 (6.8)
Native Hawaiian or Pacific Islander	1 (0.2)
Other	3 (0.5)
Baseline VAS	
Mean (SD)	62.2 (18.8)
Median	64.0
Minimum-maximum	2.0-100.0

G-GR indicates gastroretentive gabapentin; VAS, Visual Analog Scale.

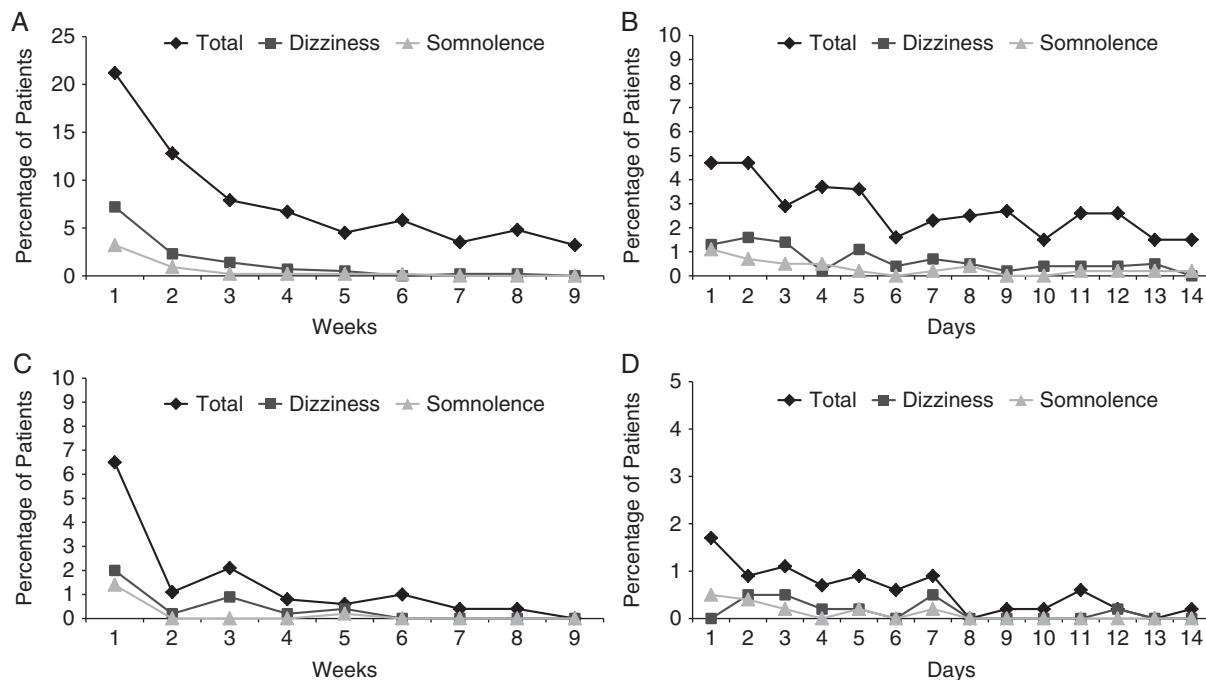
TABLE 3. Summary of Adverse Events

Preferred Term (n [%])	G-GR 1800 mg/d (n = 556)
Patients with ≥ 1 AE	296 (53.2)
Mild	137 (24.6)
Moderate	129 (23.2)
Severe	30 (5.4)
Most common AEs*	
Dizziness	66 (11.9)
Somnolence	27 (4.9)
Headache	22 (4.0)
Nausea	19 (3.4)
Diarrhea	17 (3.1)
Edema, peripheral	16 (2.9)
Dry mouth	14 (2.5)
Patients with ≥ 1 AE during titration	189 (34.0)
Patients with ≥ 1 AE leading to study discontinuation	72 (12.9)
Mild	16 (2.9)
Moderate	43 (7.7)
Severe	13 (2.3)
Most common AEs leading to discontinuation†	
Dizziness	20 (3.6)
Somnolence	9 (1.6)
Nausea	6 (1.1)
Patients with ≥ 1 AE leading to study discontinuation during titration	42 (7.6)
≥ 1 serious AEs	13 (2.3)
Mild	1 (0.2)
Moderate	5 (0.9)
Severe	7 (1.3)

\*Occurring in ≥ 2% of patients.

†Occurring in ≥ 1% of patients.

AE indicates adverse event; G-GR, gastroretentive gabapentin.



**FIGURE 2.** Adverse events (AEs) over time. AE reporting (A) by week throughout the entire study, and (B) by day during the 2-week titration period. Discontinuations due to AEs (C) by week throughout the entire study, and (D) by day during the 2-week titration period.

of AEs during week 1-2, significant predictive factors were nonwhite race (nonwhite were 2.1 times more likely to report AEs than whites at  $P = 0.0082$ ), and the BPI least pain score at baseline ( $P = 0.0549$ ). There were no significant predictive factors for occurrence of AEs after week 2. For discontinuations due to AEs, patient demographics were not predictive factors in either model 1 or model 2. In contrast, in model 2, experiencing moderate or severe AEs ( $P < 0.0001$  and  $P = 0.0006$ , respectively), common AEs ( $P = 0.028$  to  $P = 0.0394$ ), and BPI mood score at baseline ( $P = 0.0546$ ) were predictive of study discontinuations (Table 5).

To predict probabilities for reporting any AE or discontinuing due to AEs, univariable regression analyses were performed. In general, the results confirmed the analysis of predictive factors. Across all demographic groups, the predicted probabilities for occurrence of AEs at any time were 0.4 to 0.6, whereas for week 1-2 and after week 2, they were 0.2 to 0.4 (Fig. 4A). The probabilities to report any AE were different between females and males—0.6 for females versus 0.4 for males for reporting AEs at any time, 0.4 versus 0.2 for reporting any AE during week 1-2, and 0.4 versus 0.3 for reporting any AE after week 2. The probability to report any AE by nonwhite patients was higher during week 1-2 when compared with white patients (0.4 vs. 0.3), whereas the probabilities were similar after week 2. There were no differences between patients less than 75 years and 75 years and older in reporting AEs. For discontinuations due to AEs, most predicted probabilities were low—approximately 0.1 across all demographic groups, and also for experiencing mild AEs (Fig. 4B). However, the predicted probabilities were higher for patients experiencing moderate or severe AEs (0.4 and 0.5, respectively).

In support of regression analyses, population analyses for reporting AEs or discontinuing due to AEs for

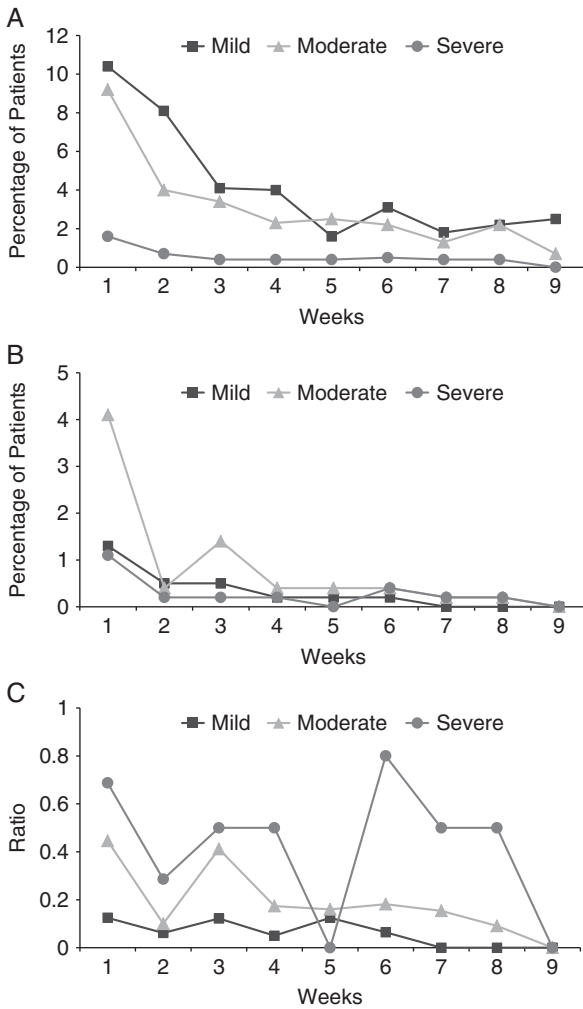
demographic groups (age, sex, and race) were analyzed by week. Consistent with the regression analyses, there were no differences between patients 75 years and older and less than 75 years in reporting any AEs (Fig. 5A). However, females reported more AEs than males during most weeks (Fig. 5B), and nonwhite patients reported more AEs than white patients during week 1-2 (Fig. 5C). The analysis of discontinuations due to AEs by week was also consistent with the analysis of predictive factors and showed no differences among groups divided by age (Fig. 5D), sex (Fig. 5E), and race (Fig. 5F).

### DISCUSSION

Both the complex character of neuropathic pain and the older age of most patients complicate the management of PHN. Advanced age is often associated with comorbidities and polypharmacy, and thus patients with PHN may be more susceptible to potentially harmful drug-drug interactions and adverse effects associated with therapeutics. Such issues may in turn limit the successful outcome of PHN treatment. Because gabapentinoids have low propensity for interactions with other drugs as they are renally excreted, this class of therapeutics is an attractive option among treatments available for PHN.<sup>32</sup>

Although gabapentinoids have generally a good safety profile, the rates of most common AEs, dizziness, and somnolence, can be relatively high for some of them, leading to relatively high rates of treatment discontinuations and interference with patient functioning. However, the current analysis of integrated data from placebo-controlled and open-label studies, as well as data from each individual clinical program,<sup>29,31</sup> demonstrated relatively low incidence of dizziness and somnolence in patients treated with 1800 mg G-GR once-daily (dizziness, 11.9%;





**FIGURE 3.** Adverse events (AEs) over time by severity. A, AE reporting, and (B) study discontinuations due to AEs by week, grouped by the severity of AEs (mild, moderate, or severe). C, The ratio of discontinuations due to AEs and AE reporting grouped by the severity of AEs.

somnolence, 4.9%). These rates decreased rapidly during the 2-week titration period to sustained low levels ( $\leq 0.7\%$  per week) after 2 to 3 weeks of treatment.<sup>29,31</sup> Furthermore, the incidence of treatment discontinuations due to dizziness (3.6%) or to somnolence (1.6%) was also low, and most of these discontinuations took place during the first week of titration. In contrast, in placebo-controlled trials of immediate-release gabapentin in patients with PHN, dosage-dependent (1800 to 3600 mg/d) rates of dizziness were 24% to

33%, and rates of daytime somnolence were 17% to 27%.<sup>23,24</sup> Dosage-dependent (1200 to 3600 mg/d) incidences of dizziness and somnolence for the extended-release formulation of gabapentin (gabapentin enacarbil) in placebo-controlled trials were 17% to 30% and 10% to 14%, respectively.<sup>33</sup> Even though peak concentrations for once-daily G-GR are numerically higher than for thrice-daily immediate-release gabapentin,<sup>34</sup> the better tolerability profile of the gastroretentive formulation may be due to more consistent gabapentin plasma levels, and/or the fact that once-daily dosing of G-GR with the evening meal leads to peak plasma concentrations during the period when most patients are asleep. However, various formulations of gabapentin were not directly compared in the efficacy studies, and we cannot exclude the possibility that other differences between the studies contributed to differences in the AE profiles.

Some gabapentinoids may require long titration periods to effective dosages and multiple daily dosing. For example, it was demonstrated that only 14% of patients taking immediate-release gabapentin reached the target dosage (1800 mg/d) after approximately 10 weeks of titration, and 27% of patients required 9 weeks to reach therapeutic dosages of pregabalin ( $\geq 300$  mg/d; the dosage equivalent to 1800 mg of G-GR or immediate-release gabapentin).<sup>15</sup> In contrast, 91.7% of patients were able to achieve the 1800-mg dose of G-GR during the 2-week titration in phase 3 and 4 trials. Although not directly compared, the differences in the effectiveness of titration between G-GR and other gabapentinoids may stem from simpler dosing for G-GR, the fact that patients are provided with a titration pack for G-GR allowing better compliance with titration, and/or from differences in the incidence of AEs. In the current study, the completion rate for titration with G-GR was high despite the fact that the incidence of AEs was also highest during the 2-week titration. However, it is important to note that the incidence of AEs decreased rapidly to sustained low levels after the titration period. Furthermore, although study discontinuations due to AEs were also highest during that period, only 22% of patients who reported AEs during titration discontinued the study. Therefore, lower incidence of AEs after the titration period was not due to the fact that most patients who could not tolerate AEs discontinued the study early but rather because of the fact that patients developed tolerance to AEs over time. These observations suggest a crucial role of the titration period in the treatment of PHN with G-GR, and if patients are informed about the G-GR tolerability profile and much lower incidence of AEs after titration, they may be more successful in completing the titration and reaching the therapeutically effective dosage.

The relative influence of various risk factors for AEs in patients with PHN or other neuropathic pain syndrome has not been well studied. Here, we report that female sex was a significant predictor of reporting any AEs at any time

**TABLE 4.** Predictive Factors\* for Occurrence of Adverse Events, Model 1

Dependent Variable	Time Period	Events (n [%])	Predictive Factor	OR (95% CI)	P
Occurrence of any AE	Any time	296 (53.2)	Sex (female vs. male)	1.83 (1.30-2.59)	0.0006
			Sex (female vs. male)	1.81 (1.23-2.66)	0.0027
	Week 1-2	172 (30.9)	Race (nonwhite vs. white)	1.83 (1.11-3.03)	0.0188
			Sex (female vs. male)	1.48 (1.02-2.14)	0.0397
	After week 2	183 (32.9)			

\*Predictive factors at significance level of  $P \leq 0.05$ . AE indicates adverse event; CI, confidence interval; OR, odds ratio.

**TABLE 5.** Predictive Factors\* for Occurrence of Adverse Events and Discontinuations Due to Adverse Events, Model 2

Dependent Variable	Time Period	Events (n [%])	Predictive Factor	OR (95% CI)	P
Occurrence of any AE	Any time	289 (53.2)	Sex (female vs. male)	1.88 (1.31-2.69)	0.0006
			Sex (female vs. male)	1.94 (1.29-2.93)	0.0015
	Week 1-2	168 (30.9)	Race (nonwhite vs. white)	2.07 (1.21-3.55)	0.0082
			Baseline BPI least pain	0.88 (0.77-1.00)	0.0549
Discontinuations due to AEs	After week 2	178 (33.1)	NA	NA	NA
	Any time	71 (13.1)	Moderate AEs (yes vs. no)	8.64 (4.42-16.89)	< 0.0001
			Severe AEs (yes vs. no)	5.37 (2.01-14.00)	0.0006
			Dizziness (yes vs. no)	3.17 (1.49-6.75)	0.0028
			Somnolence (yes vs. no)	4.22 (1.49-11.97)	0.0068
			Nausea (yes vs. no)	4.93 (1.24-19.63)	0.0235
			Headache (yes vs. no)	3.52 (1.06-11.64)	0.0394
			Baseline BPI mood	0.83 (0.68-1.00)	0.0546

\*Predictive factors at significance level of  $P \leq 0.05$ .

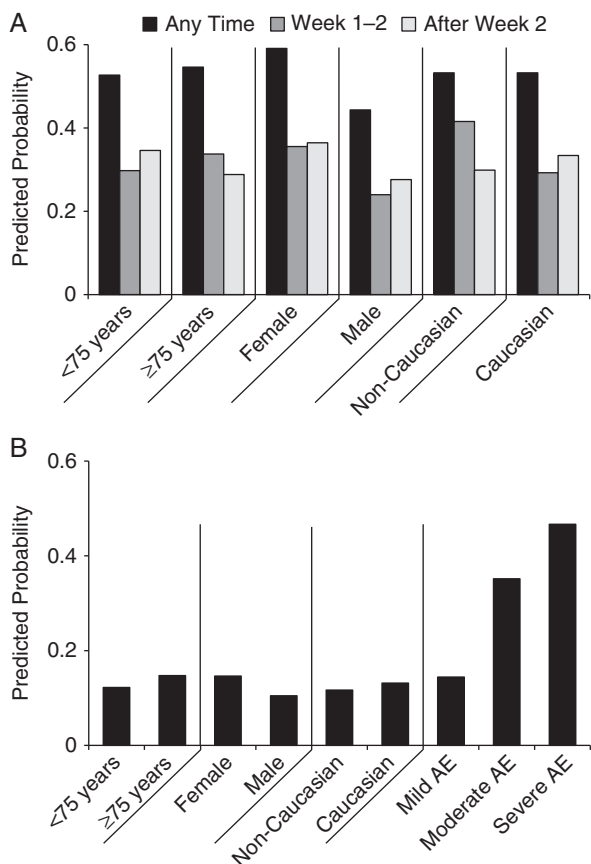
AE indicates adverse event; BPI, Brief Pain Inventory; CI, confidence interval; OR, odds ratio.

during the study, during titration period (week 1-2), or after titration; and nonwhite race was a significant predictor during titration. Also, both sex and race remained

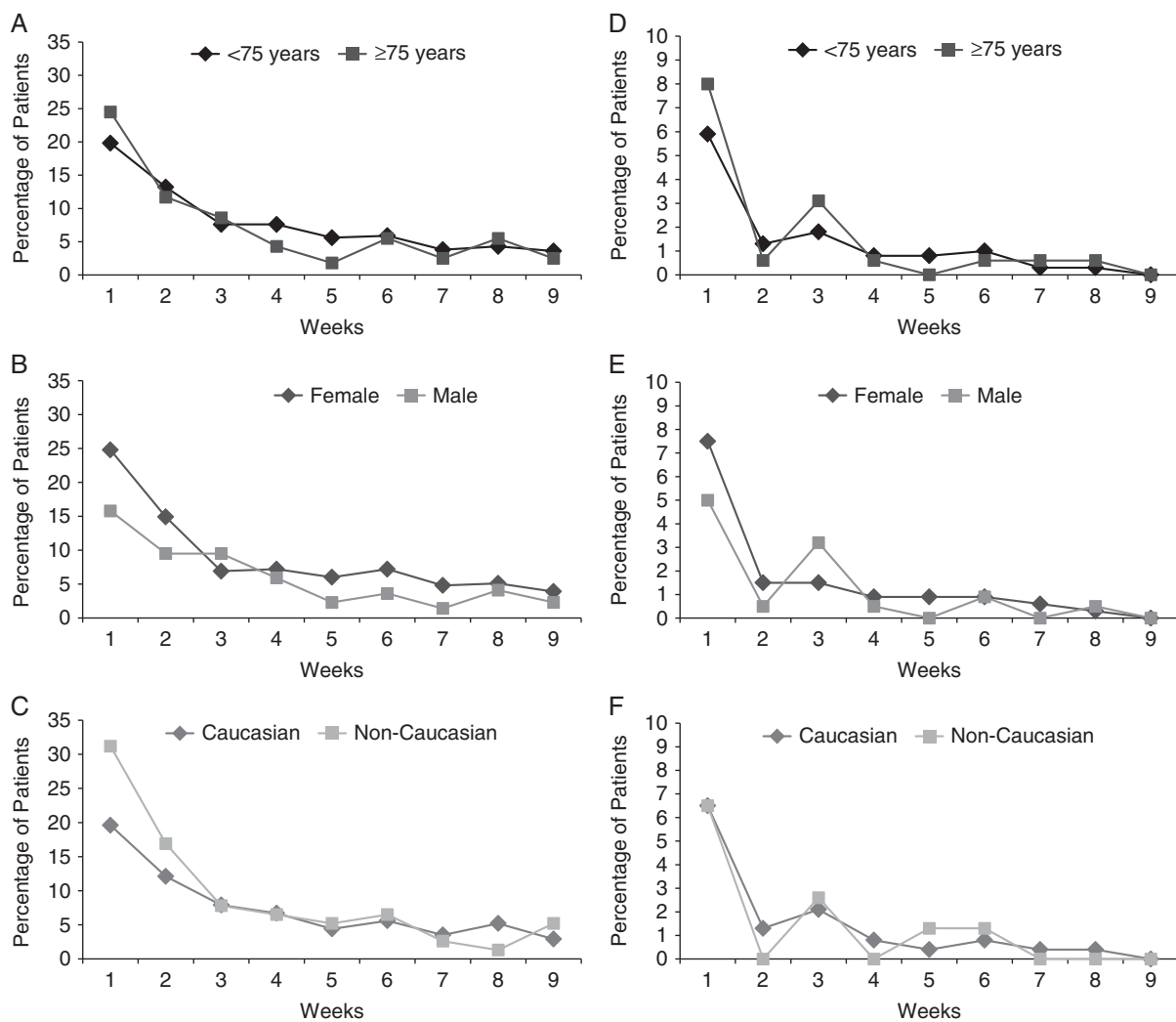
significant risk factors for AE reporting when regression analyses were adjusted for baseline pain and quality-of-life values on the VAS and BPI, suggesting that pain intensity is not an important factor. These results are in agreement with previously published reports that women experience more side effects due to treatment with therapeutic drugs than men.<sup>35,36</sup> Differences in pharmacokinetics, pharmacodynamics, and body weight have been offered as possible explanations for this phenomenon, as have hormonal effects and relative difference in dosage compared with body weight between men and women, although this has been questioned in some reports.<sup>36</sup> In addition, genetic factors related to ethnic background and race have been reported and may have an effect on drug-metabolizing enzymes, drug transporters, and receptors.<sup>37,38</sup> However, in the current analysis, the number of nonwhite patients was much lower than that of white patients, and more data are needed to support a statement regarding the distribution of adverse reactions by race for G-GR.

Importantly, patient age was not a significant factor for reporting AEs at any time throughout the study. This finding contrasts with previously published analyses of opioid use in patients with various pain symptoms, where age was the common risk factor associated with side effects.<sup>39,40</sup> This difference may stem from the fact that patients with CrCl levels of  $< 50$  mL/min were excluded from the 2 phase 3 studies of G-GR and only the phase 4 study included exclusion criteria limited to the product label (patients with CrCl levels of  $< 30$  mL/min were excluded). Although kidney function generally declines with increasing age,<sup>41</sup> it does not appear that older patients were excluded from the studies as 64.4% of patients were older than 65 years and 29.3% were 75 years and older of age. However, findings of the current study may only apply to older adults with good kidney function, and thus age may not show as a significant factor.

None of the demographic factors (age, sex, nor race) was predictive of discontinuation due to an AE; rather the severity of AEs (moderate or severe) was the strongest predictor. Importantly, although reporting more AEs, females did not discontinue G-GR treatment due to AEs more often than men, which extends our knowledge on the role of sex in reporting adverse effects versus discontinuing treatment due to these adverse effects.<sup>35,36</sup> Generally, these results suggest that the tolerability of G-GR is not affected by patient age, sex, or race, but primarily by severity of reported AEs. To



**FIGURE 4.** Predicted probabilities for adverse events (AEs) occurrence and discontinuations due to AEs. A, Predicted probabilities for patients less than 75 years and older, females, males, nonwhite, or white to report any AE at any time, during week 1-2, and after week 2. B, Predicted probabilities to discontinue the study due to AEs at any time by patients less than 75 years, 75 years and older, females, males, nonwhites, and whites, and by those who reported mild, moderate, or severe AEs.



**FIGURE 5.** Adverse events (AEs) over time by patient demographics. AEs reporting (A) by age (less than 75 vs. 75 y and older), (B) by sex (female vs. male), (C) by race (white vs. nonwhite). Study discontinuations due to AEs by (D) age, (E) sex, and (F) race.

our knowledge, there are no other analyses of AE reporting versus discontinuations due to AEs in patients with PHN or other pain syndromes. As our results show different risk factors for these 2 events, more studies are needed to better understand an important connection between experiencing AEs and discontinuing the treatment due to AEs.

One possible limitation of the current analysis is that it examined the safety and tolerability of G-GR for a limited treatment period (10 wk in the phase 3 studies and 8 wk in the phase 4 study), whereas the duration of PHN varies widely and may last for months.<sup>1</sup> However, the clinical history of the immediate-release formulation of gabapentin in the treatment of neuropathic pain as well as the safety of the gastroretentive technology<sup>26,42</sup> are extensive and well established. Furthermore, the evaluation of long-term safety and tolerability of G-GR revealed that, after reduction in AE incidence after 2-week titration period, the frequency, intensity, and severity of AEs did not change with long-term treatment.<sup>43</sup> Although patients who had not previously responded to gabapentin at daily doses >1200 mg were excluded from the phase 3 studies, exclusion criteria in the phase 4 study were limited to only those in the product label; thus the integrated patient

population was not enriched with patients likely to be tolerant of gabapentin.

In summary, the analysis of integrated data from the phase 3 and 4 studies demonstrated that the tolerability of G-GR did not appear to be affected by patient age, and although being female was predictive of reporting more AEs, it did not influence treatment discontinuations. Given that PHN is a disease for which the risk and duration of PHN increases with being older and with being female, the safety profile of G-GR appears to be well suited to this population. Although the occurrence of AEs was highest during the 2-week titration, almost all patients reached the therapeutic dosage of 1800 mg/d G-GR, which is the key for providing adequate pain relief. Thus, once-daily G-GR has the potential to provide a well-tolerated, convenient, and effective treatment option for patients with PHN, including those who are at most at risk of developing PHN.

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