

Neuropathic pain responds better to increased doses of pregabalin: an in-depth analysis of flexible-dose clinical trials

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Background: Pregabalin is an effective treatment option for many patients with neuropathic pain. Higher doses of pregabalin have been shown to be more effective in improving pain outcomes but, in practice, failing to appropriately increase the dose can leave patients under-treated.

Methods: This was a pooled analysis of 6 flexible-dose clinical trials of pregabalin in patients with neuropathic pain (diabetic peripheral neuropathy, peripheral herpetic neuralgia, posttraumatic pain, or postsurgical pain). Patients were divided into “dose pathway” groups based on their weekly pregabalin dose from the start of their trial to the first week of their maintenance phase. These were: 150 mg/day only; 150 to 300 mg/day; 150 to 300 to 450 mg/day; 150 to 300 to 450 to 600 mg/day; 150 to 300 to 600 mg/day; 300 to 600 mg/day. Pain outcomes assessed for each group at each new dose were proportion of 30% and 50% responders ($\geq 30\%$ or $\geq 50\%$ reduction in mean pain score from baseline) and mean change in pain score. Percent change in mean pain score from baseline was assessed using a marginal structural model.

Results: Seven hundred and sixty-one patients treated with flexible-dose pregabalin were included in the analysis. For each dose pathway group, there was a notably greater proportion of 30% and 50% responders and change in pain score, at each escalating dose. As assessed by the marginal structural model, higher doses of pregabalin were estimated to result in a significantly greater change in mean pain score at each week. This dose response with flexible-dose pregabalin was consistent with that previously observed with fixed-dose pregabalin.

Conclusion: Many patients who do not respond to lower doses of pregabalin will respond with notable improvements in pain outcomes when the dose is escalated. These data should encourage physicians treating patients with neuropathic pain to escalate pregabalin to the dose that delivers optimal analgesia and tolerable side effects.

Keywords: neuropathic pain, pregabalin, dosing

Introduction

Neuropathic pain, defined as “pain arising as a direct consequence of a lesion or disease affecting the somatosensory system”¹ is a common chronic pain condition. The condition represents a significant burden on patients and healthcare systems, and can be challenging to diagnose and effectively treat.^{2,3} Despite the availability of a number of effective pharmacological treatment options,⁴ many patients with neuropathic pain, particularly those with more severe conditions, may be untreated or undertreated.⁵

Pregabalin (Pfizer, New York, USA), an $\alpha_2\delta$ ligand, is indicated in the USA for the treatment of diabetic peripheral neuropathy (DPN), peripheral herpetic neuralgia (PHN), and spinal cord injury,⁶ and in Europe for the treatment of peripheral and central neuropathic pain.⁷ It is recommended as a first-line treatment for diverse neu-

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ropathic pain conditions (including DPN, PHN, and central pain) by the European Federation of Neurological Societies,⁴ the International Association for the Study of Pain,⁸ and the American Academy of Neurology.^{9,10} While pregabalin is not effective in every patient with neuropathic pain, its efficacy has been demonstrated in clinical trials and meta-analyses.¹¹ Cumulatively, it is estimated that there have now been over 34 million patient-years of exposure to pregabalin.¹²

A meta-analysis of clinical trials of different treatments for the neuropathic pain condition DPN concluded that pregabalin at doses ≥ 300 mg/day was more effective in improving pain than pregabalin at doses ≤ 150 mg/day,¹³ although many patients do respond to treatment with pregabalin at lower doses (≤ 300 mg/day).^{13,14} As a consequence, it is recommended that in clinical practice, pregabalin should be carefully escalated to the dose that delivers optimal analgesia and tolerable side effects.^{4,6,15} Despite this, some physicians may not attempt a higher dose of pregabalin in patients who do not respond at an initial low dose and many patients receive doses ≤ 150 mg/day.¹⁶

New evidence showing that there are patients who do not respond to a low dose of pregabalin but who do subsequently respond when the dose is increased may help to provide clearer guidance to physicians and more effective treatment to patients. This analysis pooled individual patient-level data from 6 randomized, placebo-controlled studies of flexible-dose pregabalin in neuropathic pain with the aim of assessing how patients who do not initially respond to pregabalin at lower doses react to increasing doses.

Methods

Source data

This analysis included all Pfizer-sponsored studies of pregabalin completed at the time the analysis started that met the following criteria: randomized, parallel, placebo-controlled; conducted in patients with neuropathic pain; and included a treatment arm of flexible-dose pregabalin (150 to 600 mg/day). Only Pfizer-sponsored studies were included as patient-level data were required for the analysis. A total of 6 trials met these criteria. A 12-week trial conducted in 406 patients with DPN, A0081030 (ClinicalTrials.gov: NCT00156078).¹⁷ A 4-week trial conducted in 269 patients with PHN, A0081004 (NCT00159666).¹⁸ A 12-week trial conducted in 338 patients with either DPN or PHN, 1008–1155.¹⁹ An 8-week trial conducted in 308 patients with either DPN or PHN, A0081081 (NCT00301223).²⁰ An 8-week trial conducted in 254 patients with posttraumatic or postsurgical (PT/PS) pain, A0081064 (NCT00292188).²¹ An 8-week trial conducted in 240 patients with DPN, PHN, or PT/PS,

A0081037 (NCT00141219).²² Some historical trials are not recorded at ClinicalTrials.gov.

The trials were conducted between July 2001 and May 2008 and included patients from Asia, Europe, the Middle East, and North and South America. The primary efficacy outcome in each study was the change in mean pain score at endpoint compared with placebo. Mean pain score was the mean score over the past 7 days as recorded by patients in a daily pain diary and measured using an 11-point numeric rating scale scored from 0 (no pain) to 10 (worst possible pain).

Data on the pain response to fixed-dose pregabalin were taken from all Pfizer-sponsored, randomized, placebo-controlled trials of pregabalin in patients with neuropathic pain. This was a total of 27 trials: 1008–1014,²³ 1008–1029,²⁴ 1008–1030,²⁵ 1008–1040,²⁵ 1008–1045,²⁶ 1008–1125,²⁷ 1008–1127,²⁸ 1008–1131,²⁹ 1008–1149,³⁰ 1008–1155,¹⁹ 1008–1196,³¹ A0081004 (ClinicalTrials.gov: NCT00159666),¹⁸ A0081030 (NCT00156078),¹⁷ A0081037 (NCT00141219),²² A0081060 (NCT00159679),³² A0081064 (NCT00292188),²¹ A0081066,³³ A0081071 (NCT00143156),¹⁷ A0081081 (NCT00301223),²⁰ A0081107 (NCT00407745),³⁴ A0081120 (NCT00394901),³⁵ A0081163 (NCT00553475),³⁶ A0081244 (NCT01049217),³⁷ A0081265 (NCT01332149), A0081268 (NCT01455415),³⁸ A0081269 (NCT01474772),³⁹ and A0081276 (NCT01455428).⁴⁰ Some historical trials are not recorded at ClinicalTrials.gov.

The protocol for each trial adhered to the International Ethical Guidelines for Biomedical Research Involving Human Subjects, the International Conference on Harmonisation Good Clinical Practice guidelines, and the Helsinki Declaration. All trials were approved by the appropriate independent ethics committee and all patients provided written informed consent.

Dose pathway groups

To be included in this analysis, patients had to have $\geq 80\%$ compliance on the study drug (calculated by total number of days on a valid dose/duration of treatment), to have remained in their study for at least 28 days, and to have been receiving a stable dose of pregabalin for at least 4 days. Patients were grouped into dose pathways based on the pattern of their pregabalin dose at each week during titration phase and up to 1 week of their maintenance phase. The dose pathway groups were: 150 mg/day only; 150 to 300 mg/day; 150 to 300 to 450 mg/day; 150 to 300 to 450 to 600 mg/day; 150 to 300 to 600 mg/day; and 300 to 600 mg/day. Each patient was included in a single-dose pathway group. Patients who decreased their dose at any visit or who did not remain at the particular dose level for at least 4 days were not included in a dose pathway group.

Statistical analysis

Descriptive statistics were used to describe outcomes in treatment-compliant and non-compliant patients for each dose pathway. Assessed outcomes included: proportion of 30% responders (patients with $\geq 30\%$ reduction in mean pain score from baseline); proportion of 50% responders (patients with $\geq 50\%$ reduction in mean pain score from baseline); and mean change in pain score at each new dose. A $\geq 30\%$ reduction in mean pain score from baseline, or a 2-point change in pain score, was accepted to represent a clinically important difference.^{41,42} For the descriptive analysis, patients were also required to have had $\geq 80\%$ compliance on pregabalin over the entire study.

In addition, the percent change in mean pain score from baseline was assessed using a marginal structural model (MSM).^{43,44} A MSM was selected for this analysis as it can accommodate both multiple time-independent covariates, such as baseline clinical and demographic variables and time-dependent covariates, such as treatment and treatment outcomes, even in the presence of missing data and time-varying confounders, as is the case in flexible-dose studies. Specifically, the MSM was a weighted repeated-measures approach using treatment as a time-varying covariate in which weights, based on inverse probability of treatment weighting, control for time-dependent confounders. This produced a pseudo-population with balance in both time-invariant and time-varying covariates that allowed for causal treatment comparisons using standard repeated-measure models. The weighting could also be adjusted to incorporate adjustments for missing data that provides validity under missing at random. Patients were included in the MSM analysis regardless of their level of treatment compliance but a separate analysis limited to patients with $\geq 80\%$ compliance on pregabalin was conducted for comparison. As a sensitivity analysis, an unweighted estimate of the change in mean pain score from baseline was also conducted. The MSM-estimated change with flexible-dose pregabalin conducted in this analysis was also compared directly with the estimated change in mean pain score from baseline with fixed-dose pregabalin. The study conducted in PHN patients alone, A0081004 (NCT00159666),¹⁸ was included in the descriptive analysis but not in the MSM-estimated models as the length of the study was only 4 weeks (compared with 8 or 12 weeks for all other studies).

Results

Patient population

A total of 889 patients were treated with flexible-dose pregabalin; 761 of which met the inclusion criteria ($\geq 80\%$ compliance on pregabalin, had remained in their study for

≥ 28 days, and receiving a stable dose of pregabalin for ≥ 4 days) and were included in the descriptive analysis. Of these, 717 could be grouped into one of the six established dose response pathways. The demographic characteristics and baseline clinical characteristics of patients were broadly similar regardless of treatment compliance (Table 1).

Improvement in pain outcomes in each dose pathway

Cumulative assessment of the proportion of 30% (Figure 1) and 50% (Figure 2) pain responders for each dose pathway

Table 1 Baseline demographic and clinical characteristics

Characteristic	Pregabalin (all patients)	Pregabalin ($\geq 80\%$ compliant)
N	889	761
Female, n (%)	489 (55.0)	413 (54.3)
Male, n (%)	400 (45.0)	348 (45.7)
Race, n (%)		
White	327 (36.9)	264 (34.7)
Asian	503 (56.6)	444 (58.3)
Black	9 (1.0)	8 (1.1)
Other	50 (5.6)	45 (5.9)
Age, years		
Mean (SD)	58.5 (11.0)	58.8 (10.5)
Median	59.0	60.0
Baseline pain score		
Mean (SD)	6.4 (1.6)	6.3 (1.6)
Median	6.3	6.3

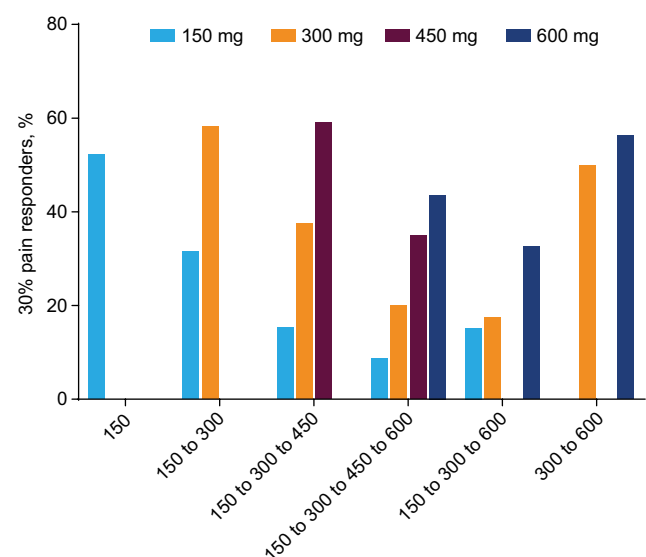


Figure 1 Cumulative proportion of 30% pain responders by dose for each dose pathway. **Note:** Cumulative percentage of patients with a $\geq 30\%$ reduction in mean pain score from baseline at each new dose for each dose pathway group shows an increased 30% responder rate with increasing dose of pregabalin.

showed that across every dose pathway, there was recruitment of new pain responders (30% or 50%) at each new and higher dose of pregabalin. Table 2 shows the number (and proportion) of 30% responders at each dose limited to only those patients who were non-responders at the previous dose in their dose pathway (i.e., non-cumulative data). For example, in the 150 to 300 mg/day dose pathway, 100 (of 146) patients were non-responders at 150 mg/day. When

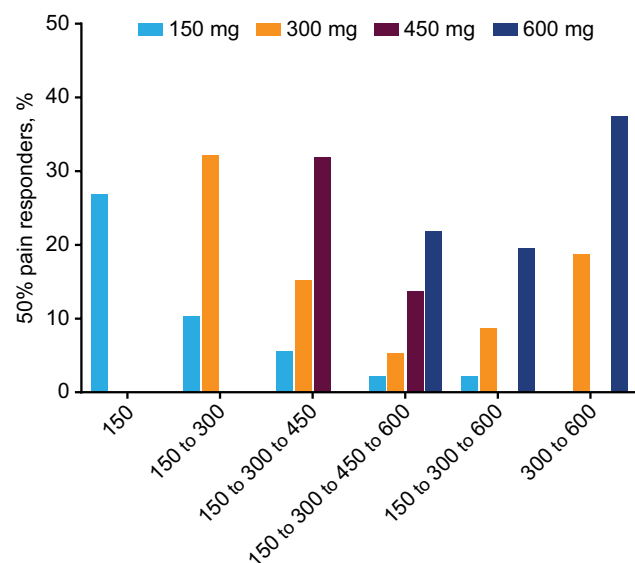


Figure 2 Cumulative proportion of 50% pain responders by dose for each dose pathway.

Note: Cumulative percentage of patients with a $\geq 50\%$ reduction in mean pain score from baseline at each new dose for each dose pathway group shows an increased 50% responder rate with increasing dose of pregabalin.

these patients were escalated to 300 mg/day, a further 43 (of the 100 non-responding) patients were responders (Table 2). An equivalent pattern was observed with 50% responders (Table 3). These data demonstrate that for every dose pathway, previously non-responsive patients would become 30% or 50% responders with every increase in pregabalin dose.

The change in pain score from baseline for each dose pathway indicated that patients in the shorter dose pathways (i.e., those who remained on 150 mg/day or only escalated to 300 mg/day) had a notable larger change in pain score with pregabalin 150 mg/day (and 300 mg/day) than did those patients who subsequently went on to be escalated to higher doses (Table 4). This finding reflects the fact that patients with a greater response at lower doses were less likely to be escalated to a higher dose. At the same time, for those patients who were escalated to a higher dose, there was a notably greater change in pain score at each escalating dose (Table 4).

These data exclude non-compliant patients (those with $< 80\%$ compliance on pregabalin over the entire study). Considering only patients who were non-compliant for all dose pathways combined, there was a notably lower proportion of 30% (32.3%) and 50% (15.2%) responders than for treatment-compliant patients (Figures 1 and 2).

Weighted estimation of change in pain score for each dose

As assessed by MSM, higher doses of pregabalin were estimated to result in a significantly greater change in mean pain

Table 2 Thirty percent responders at each dose for each dose pathway

Dose pathway	150 mg/day		300 mg/day		450 mg/day		600 mg/day	
	N ^a	n (%) ^b	N ^a	n (%) ^b	N ^a	n (%) ^b	N ^a	n (%) ^b
150 mg/day								
Responder	67	35 (52.2)	–	–	–	–	–	–
Non-responder		32 (47.8)						
150 to 300 mg/day								
Responder	146	46 (31.5)	100	43 (43.0)	–	–	–	–
Non-responder		100 (68.5)		57 (57.0)				
150 to 300 to 450 mg/day								
Responder	144	22 (15.3)	122	36 (29.5)	86	31 (36.1)	–	–
Non-responder		122 (84.7)		86 (70.5)		55 (63.9)		
150 to 300 to 450 to 600 mg/day								
Responder	298	26 (8.7)	272	41 (15.1)	231	43 (18.6)	188	28 (14.9)
Non-responder		272 (91.3)		231 (84.9)		188 (81.4)		160 (85.1)
150 to 300 to 600 mg/day								
Responder	46	7 (15.2)	39	3 (7.7)	–	–	36	6 (16.7)
Non-responder		39 (84.8)		36 (92.3)			30 (83.3)	
300 to 600 mg/day								
Responder	–	–	16	8 (50.0)	–	–	8	2 (25.0)
Non-responder				8 (50.0)				6 (75.0)

Notes: ^aNumber of subjects available for the dose level (i.e., were non-responders at the previous dose in the dose pathway). ^bNumber (percentage) of patients who were 30% responders at that dose.

Table 3 Fifty percent responders at each dose for each dose pathway – evaluation of non-responder at low dose moving to the next dose level

Dose pathway	150 mg/day		300 mg/day		450 mg/day		600 mg/day	
	N ^a	n (%) ^b	N ^a	n (%) ^b	N ^a	n (%) ^b	N ^a	n (%) ^b
150 mg/day								
Responder	67	18 (26.9)	–	–	–	–	–	–
Non-responder		49 (73.1)						
150 to 300 mg/day								
Responder	146	15 (10.3)	131	32 (24.4)	–	–	–	–
Non-responder		131 (89.7)		99 (75.6)				
150 to 300 to 450 mg/day								
Responder	144	8 (5.6)	136	18 (13.2)	118	21 (17.8)	–	–
Non-responder		136 (94.4)		118 (86.8)		97 (82.2)		
150 to 300 to 450 to 600 mg/day								
Responder	298	8 (2.7)	290	13 (4.5)	277	25 (9.0)	252	29 (11.5)
Non-responder		290 (97.3)		277 (95.5)		252 (91.0)		223 (88.5)
150 to 300 to 600 mg/day								
Responder	46	1 (2.2)	45	4 (8.9)	–	–	41	5 (12.2)
Non-responder		45 (97.8)		41 (91.1)			36 (87.8)	
300 to 600 mg/day								
Responder	–	–	16	3 (18.7)	–	–	13	3 (23.1)
Non-responder				13 (81.3)				10 (76.9)

Notes: ^aNumber of subjects available for the dose level (i.e., were non-responders at the previous dose in the dose pathway). ^bNumber (percentage) of patients who were 50% responders at that dose.

Table 4 Mean change in pain score from baseline for each dose pathway – evaluation of non-responder at low dose moving to the next dose level

Dose	150 mg/day		150 to 300 mg/day		150 to 300 to 450 mg/day		150 to 300 to 450 to 600 mg/day		150 to 300 to 600 mg/day		300 to 600 mg/day	
	n ^a	Change ^b	n ^a	Change ^b	n ^a	Change ^b	n ^a	Change ^b	n ^a	Change ^b	n ^a	Change ^b
Based on 30% pain responders population												
150 mg/day	67	-1.92	146	-1.33	144	-0.72	298	-0.55	46	-0.50		
300 mg/day			100	-1.56	122	-1.18	272	-0.86	39	-0.46	16	-2.19
450 mg/day					86	-1.34	231	-1.02				
600 mg/day							188	-0.97	36	-0.62	8	-1.90
Based on 50% pain responders population												
150 mg/day	67	-1.92	146	-1.33	144	-0.72	298	-0.55	46	-0.50		
300 mg/day			131	-2.00	136	-1.32	290	-0.98	45	-0.77	16	-2.19
450 mg/day					118	-1.79	277	-1.35				
600 mg/day							252	-1.50	41	-1.02	13	-2.45

Notes: ^aNumber of subjects available for the next dose level (i.e., were non-responders at the previous dose in the dose pathway). ^bChange in mean pain score from baseline based on the number of subjects available at that dose level.

score at each week of assessment (Figure 3). Restricting the analysis to only those patients with $\geq 80\%$ compliance with pregabalin resulted in similar results (not shown). This was also supported by a comparison of the weighted MSM analysis with an unweighted estimate of the change in mean pain score, with each analysis showing similar results (not shown).

Direct comparison of the MSM-estimated change with flexible-dose pregabalin with the estimated change in mean pain score from baseline with data from fixed-dose clinical trials of pregabalin (a total of 3128 patients; 516 receiving pregabalin 150 mg/day, 1679 receiving pregabalin

300 mg/day, and 933 receiving pregabalin 600 mg/day) demonstrated a similar dose-response pattern for each dose of pregabalin (Figure 4).

Discussion

Pregabalin is recommended as a treatment for diverse neuropathic pain conditions^{4,8–10} where it is advised that it be carefully escalated to the optimal dose.^{4,6,15} In the USA, the maximum approved dose of pregabalin is 300 mg/day for DPN and 600 mg/day for PHN,⁶ while in Europe it is 600 mg/day for all neuropathic pain.⁴⁵ Despite this, many patients

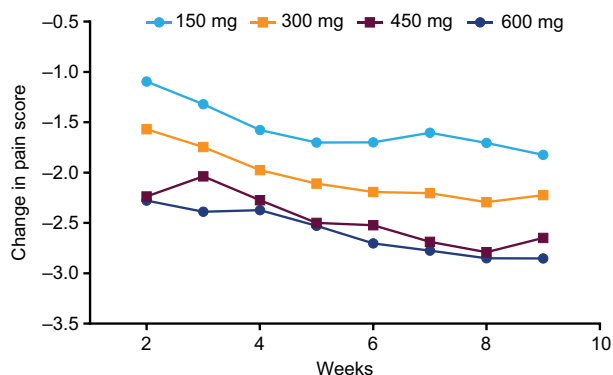


Figure 3 Estimated change in pain score from baseline by marginal structural model showing that increasing doses of pregabalin result in a greater reduction in pain score.

Notes: All doses of pregabalin significantly ($P < 0.05$) improved pain score versus 150 mg at each week with the exception of week 9 for 150 mg/day versus 300 mg/day. Change in pain score with pregabalin 450 mg/day and 600 mg/day was significantly > 300 mg/day at each week. There was no significant difference observed between 450 mg/day and 600 mg/day at any week.

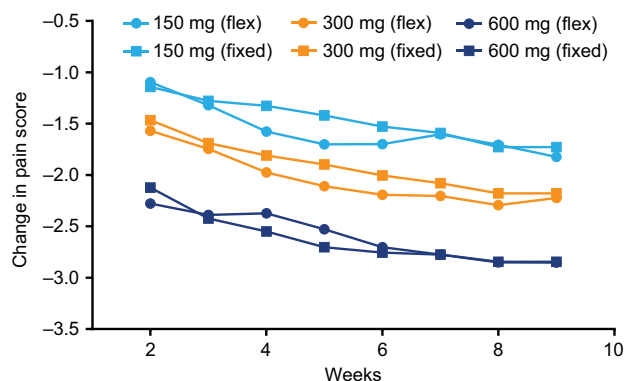


Figure 4 Dose response in flexible-dose studies of pregabalin is similar to that observed in fixed-dose studies.

Notes: Marginal structural model-estimated change in mean pain score from baseline for flexible-dose pregabalin (flex) and estimated change in mean pain score from baseline for fixed-dose pregabalin (fixed). Data shown by week for each dose.

may not receive the most effective dose of pregabalin, with a recent drug utilization study in the UK indicating that the approximate median prescribed dose of pregabalin for neuropathic pain was only 150 mg/day.¹⁶ This analysis provides evidence that new patients will tend to respond with every increase in pregabalin dose.

Neuropathic pain can be challenging to treat effectively.² While there are a number of treatment options, not all are effective in all patients. For instance, data on the efficacy of pregabalin in patients with lower back pain are inconsistent.^{46,47} In a randomized withdrawal trial, pregabalin was not shown to be effective in patients with chronic lumbosacral radiculopathy.⁴⁸ Even for those conditions where its efficacy is well established, many patients will not respond to treatment with pregabalin.¹¹ As physicians are advised to ensure

that effective and tolerable treatment for neuropathic pain is initiated as soon as possible,² it is important to ascertain quickly if a treatment is ineffective so that other options can be tested. In these circumstances, it may be understandable why the time is not taken to escalate some patients to a higher, efficacious dose of pregabalin. However, of the 701 patients in this analysis who took the 150 mg/day dosing, 136 (19.4%) responded at that dose. Of those who continued to higher doses, 231 (33.0%) responded at a higher dose. These data do not correct for the tendency for higher doses to be used when patients have inadequate response at a lower dose. The MSM analyses make some correction for this tendency in dose escalation and indicate that it can be worthwhile to persist with pregabalin until the dose that delivers optimal analgesia and tolerable side effects is utilized.

Physicians may be reluctant to escalate the dose of pregabalin due to concerns about adverse events. A previous analysis described the incidence of common adverse events with each dose of pregabalin.⁴⁹ In that analysis, the incidence of most adverse events was higher with higher fixed doses (450 or 600 mg/day) of pregabalin.⁴⁹ However, the incidence of adverse events with flexible-dose pregabalin was lower than with any fixed dose > 150 mg/day.⁴⁹ In addition, most adverse events emerged soon after the start of treatment and resolved within 1–2 weeks.⁴⁹ It was advised that potential adverse events with pregabalin be discussed with patients, before and during treatment, as greater awareness of what to expect could help manage expectations.⁴⁹ Together with the data reported here, this suggests that communication and careful dose titration could result in improved pain outcomes for patients.

Fixed dose studies have previously demonstrated a clear dose response with pregabalin.^{11,13} In these studies, patients were assigned to a specific fixed dose prior to treatment with the dose response being shown for a population of patients. Here, for the first time, this analysis shows that this dose response also exists for flexible-dose pregabalin, with individual patients being shown to respond to increasing doses. This dose response was shown to be broadly equivalent in the direct comparison between flexible- and fixed-dose pregabalin shown in Figure 4. This may suggest that in the future, some initial fixed-dose clinical trials could theoretically be replaced with flexible-dosing trials that would allow for fewer treatment arms. However, this would require additional data, and confirmation with other treatments and in other patient groups before it could be considered. While a previous analysis also used a MSM to evaluate dose-response in inflexible-dose trials of an antipsychotic, the analysis did not directly compare this

with data from fixed-dose trials.⁵⁰ We are not aware of any comparable analysis for any treatment for neurological pain.

Limitation

The descriptive part of this analysis was limited to those patients who were $\geq 80\%$ compliant with treatment. As would be expected, there was a notably lower rate of efficacy among those patients who were $< 80\%$ compliant. As these patients could not be considered representative of patients treated with the designated dose, they were excluded from the analysis. As a result, the proportion of patients responding at each dose in this analysis may be overstated relative to the full population. This could be considered a limitation of this analysis as in routine clinical practice it is likely that many patients would be $< 80\%$ compliant with treatment, emphasizing the importance of promoting treatment compliance in clinical practice. Nevertheless, the MSM analysis was conducted in both those patients who were $\geq 80\%$ compliant and in all patients together. The data for all patients are presented here (Figures 3 and 4) but the results when considering compliant patients only were equivalent.

Conclusion

The analysis demonstrates that many patients who do not respond to pregabalin at lower doses will subsequently respond when the dose is increased. Physicians are advised to follow treatment guidelines and escalate pregabalin to the dose that delivers optimal analgesia and tolerable side effects.

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Disclosure

Mark Latymer, Mary Almas, Marie Ortiz, Bruce Parsons, and Rita Prieto are employees of Pfizer and hold stock options with Pfizer. The authors report no other conflicts of interest in this work.

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