Neurol J Southeast Asia 2002; 7 : 25 – 34

Safety, tolerability, and efficacy of gabapentin in neuropathic pain: Results of a post-marketing surveillance study in 1214 Filipino patients

Ester S BITANGA MD, *Alejandro C BAROQUE MD, **Alberto S SANTOS-OCAMPO MD, **Almar Y GUEVARRA RN, **Margaret B QUERIJERO MD, ***Carlos L CHUA MD

*Philippine Neurological Association, *Santo Tomas University Hospital, **Medical Affairs Division, Pfizer Philippine, ***University of Philippine-Philippine General Hospital*

Abstract

A post-marketing surveillance study of gabapentin usage in Filipino patients with neuropathic pain was conducted. Safety, tolerability and analgesic efficacy were assessed after a minimum of two weeks of gabapentin treatment, with starting and final doses determined by the prescribing physician. Of the 1,214 patients who entered the study, 95.7% completed the minimum two weeks duration of therapy. The mean age was 54 years, and the most common neuropathic pain diagnoses were painful diabetic neuropathy (30.4%), nonspecific neuropathies (20.2%), trigeminal neuralgia (12.8%), central pain after stroke (8.8%), and post-herpetic neuralgia (8.4%). Ninety-two percent of patients were maintained within a dose range of 300mg/day to 1200mg/day. The incidence of adverse events was 6%, and consisted mostly of somnolence and dizziness, with 76% of patients reporting "very good" to "excellent" tolerability. There were 34 documented dropouts (2.9%), of which only seven (0.6%) were thought to be related to an adverse event from gabapentin. Visual analog scale pain scores declined significantly from a mean of 67.8 $\pm$ 20 mm at baseline, to 16.1 $\pm$ 15mm after treatment ($p < 0.05$). In conclusion, gabapentin at 300mg/d to 1200mg/d is well tolerated and efficacious among Filipino patients with various neuropathic pain syndromes.

INTRODUCTION

Neuropathic pain involves a spectrum of chronic pain syndromes caused by injury or disease of the peripheral or central nervous system.[1,2] In contrast to nociceptive pain, neuropathic pain is pathological, offers no biologic advantage, and causes suffering and distress.[1] Neuropathic pain syndromes involve multiple etiologies, including metabolic, traumatic, ischemic, toxic, infectious and immune-mediated insults.[1] Even within each syndrome, different causative mechanisms may be at work.[1-3]

Until recently, oral drug therapy for neuropathic pain has been disappointing. Non-steroidal anti-inflammatory drugs are generally not effective, while opiates carry long-term risks of habituation with chronic use.[1-4] Tricyclic antidepressants commonly cause troublesome cardiovascular side effects such as arrhythmias and postural hypotension, and autonomic side effects such as blurred vision, dry mouth, constipation and urinary retention.[5] Within the last decade, anticonvulsants, which act on specific neurotransmitter receptors that generate and maintain hyperexcitability, have been increasingly used for the management of neuropathic pain.[2,6] Many similarities in the pathophysiologic mechanisms observed in epilepsy and neuropathic pain justify exploration of anticonvulsant usage in these complex pain syndromes.[2]

Among the newer generation of anticonvulsants, gabapentin (1-[aminomethyl]-cyclohexaneacetic acid) is probably the most promising and best studied for neuropathic pain.[2] Structurally, gabapentin is a gamma-aminobutyric acid (GABA) molecule joined to a lipophilic cyclohexane ring. By design, gabapentin was intended to mimic the action of GABA, a major inhibitory neurotransmitter of the mammalian brain. Unlike its structural analogue GABA, gabapentin was designed to cross the blood-brain barrier. It has been suggested that gabapentin may promote the increased release of GABA, as demonstrated by a magnetic resonance imaging

Address correspondence to: Alberto S. Santos-Ocampo, M.D., 23rd Floor, Ayala Life-FGU Center 6811 Ayala Avenue, Makati City 1200 Philippines + 63 2 864-3782 to 83 + 63 2 864-3788 (fax) e-mail: bersanto@yahoo.com

spectroscopy study, but its mechanism of action does not appear to be related to any effect on the GABA receptor.[2,7] Another proposed mechanism includes the binding of gabapentin to the a-2-d subunit of voltage-dependent calcium channels.[2,6] Taken together, the exact mechanisms of pain relief by gabapentin remain unclear.

Anecdotal reports, reviews, and open-label trials of the analgesic efficacy of gabapentin in neuropathic pain have been published. These include cases of multiple sclerosis, neuropathic cancer pain, reflex sympathetic dystrophies, trigeminal neuralgia, erythromelalgia, central pain syndromes and spinal cord injury pain. Clinically efficacious maintenance doses have been reported between 900 to 3600mg/day.[8-18]

Recently, three randomized controlled trials have shown that gabapentin monotherapy is efficacious for the treatment of pain in diabetic neuropathy.[19-21] In two additional randomized controlled trials, gabapentin significantly reduced average pain scores in postherpetic neuralgia.[22,23]

In the Philippines, gabapentin (Neurontin™) has received regulatory approval for use in neuropathic pain since October 1, 1998. This report reviews prospective tolerability, safety and efficacy data collected over the course of a post-marketing surveillance study in Filipino patients with various neuropathic pain syndromes. It is also the first large-scale study involving the use of gabapentin in Asian patients.

METHODS

This was an open label, prospective, non-comparative, post-marketing surveillance study of gabapentin (Neurontin™) in the treatment of various neuropathic pain syndromes. Patients were enrolled between February 1, 2001 and July 15, 2001. Neurologists, pain specialists, orthopedic surgeons, rehabilitation medicine specialists, and internists from throughout the Philippines were asked to enroll both inpatients and outpatients. In keeping with the principles of PMS studies, no patients were excluded unless they were less than 18 years old, pregnant or lactating females, or had contraindications to gabapentin based on the package insert.

Since this study was meant to reflect usual clinical practice, patients were allowed to use concomitant medications for a variety of pre-existing illnesses, provided these were not contraindicated in the package insert. Supplemental analgesics during the course of this study were also allowed.

After baseline assessments, including a history and targeted physical examination, patients were started on 300 to 1200mg/d of gabapentin. The choice of initial dose and titration of the maintenance dose was left to the discretion of the prescribing physician. Duration of therapy was a minimum of 2 weeks, after which repeat assessments were performed.

Adverse events were recorded and physicians were asked to comment on severity, suspected relationship to study drug, and outcome. Analgesic efficacy was measured at baseline (Day 1) and on the final visit (Day ≥ 14). Efficacy in pain relief was measured with the 100mm Visual Analog Scale and a 10-point ordinal Pain Intensity Scale: (*0 = no pain, 1-3 = mild pain, 4-6 = moderate pain, 7-9 = severe pain, 10 = worst measurable pain).* Patient's and Physician's overall assessments of efficacy (Excellent, Very Good, Good, Fair, Poor) were also recorded.

Results of the patients' safety and efficacy assessments were reported using descriptive statistics. Any patient who received at least one dose of gabapentin was included in the safety analysis.

RESULTS

The patients' demographic features

A total of 1,214 patients were enrolled in this study, with 95.7% completing the minimum 2-weeks duration of therapy (Table 1). The mean duration of observation was 22.3 +/- 17.7 days. Fifty-four percent were women and forty-six percent were men. The mean age of the patients was 54.1 $\pm$ 14.6 years. Majority of the patients (60.2%) were greater than 50 years of age. Painful diabetic neuropathy (30.4%), nonspecific neuropathies (20.2%), trigeminal neuralgia (12.8%), central pain after stroke (8.8%) and post-herpetic neuralgia (8.4%) were the most common diagnoses treated.

Concomitant illnesses and medications

The most commonly documented pre-existing illnesses were diabetes mellitus, hypertension, chronic obstructive pulmonary diseases, cancer, and arthropathies. (Table 2). Narcotic and non-narcotic analgesics (13.7%) and non-steroidal anti-inflammatory drugs (12.8%) were being taken by some patients prior to starting treatment with gabapentin. (Table 3).

Table 1 : The patients' demographic features and clinical diagnosis

Characteristics	**Percentage (N=1,214)**
Gender	
Male	45.6
Female	54.0
Unknown	0.4
Age (years)	
≤ 20	0.9
21-30	5.7
31-40	12.5
41-50	19.1
51-60	24.4
61-70	23.2
71-80	10.0
> 80	2.6
Unknown	1.5
Clinical Diagnosis	
Diabetic peripheral neuropathy	30.4
Peripheral neuropathy, unspecified	20.2
Trigeminal neuralgia	12.8
Central pain after stroke	8.8
Postherpetic neuralgia	8.4
Central neurogenic pain	8.3
Myelopathic pain	3.6
Reflex sympathetic dystrophy	2.3
Brain stem induced pain	0.2
Arachnoiditis	0.2
Others	17.1

Starting and final doses of gabapentin

Most patients were started between 300mg/day (57.6%) and 900mg/day (29.0%) of gabapentin, and were maintained within a total daily dose of 300mg/day (42.1%), 600mg/day (4.8%), 900mg/day (43.4%) and 1200mg/day (2.1%) by the end of the study (Figure 1). The mean final total daily dose was 613.7mg/day (range of 100 to 2100mg/day). The shift in dosing towards the higher doses at the final visit suggested that upward titration was necessary in some cases. This dose range of 300mg to 1200mg/day appeared to provide sufficient analgesic efficacy for most patients (92.4%) at the time of study termination.

Safety and tolerability of gabapentin

Of the 1214 patients who received at least one dose of study drug, 74 patients reported an adverse event (incidence of 6.0%) with 56 events (4.6%) believed to be related to the study drug. Among these, the most common were dizziness and drowsiness (Table 4A). Based on patient characteristics, adverse events were more frequently reported in men, and in patients receiving concomitant analgesics, particularly opioid (morphine sulfate, fentanyle, tramadol), and non-opioid analgesics (paracetamol), anticonvulsants (carbamazepine, phenytoin), and benzodiazepines (Table 4B). The final mean total

Table 2. Pre-existing illnesses

Disorder	Percentage (N=1,214)
Diabetes Mellitus	17.6
Hypertension	11.1
Hyperlipidemias, dyslipidemias, or obesity	6.2
Chronic obstructive pulmonary disease	1.7
Cancer	1.4
Rheumatologic, arthropathies & muscular	1.4
Infection, urinary tract	1.0
Cerebrovascular accidents	0.8
Infection, respiratory (including tuberculosis)	0.8
Chronic renal disease	0.6
Infection, viral	0.5
Headaches, including migraine	0.4
Asthma	0.4
Congestive heart failure / cardiomegaly	0.4
Anemia and hematologic abnormalities	0.3
Benign prostatic hypertrophy	0.3
Thyroid disorders	0.3
Cardiac arrhythmias	0.2
Guillan-Barre syndrome	0.2
Infection, skin and soft tissue	0.2
Peptic ulcer disease	0.2
Peripheral vascular disease	0.2
Psychiatric disorders including depression	0.2
Seizure disorders	0.2
Rheumatologic, systemic	0.1
Bell's palsy	0.1
Hyperuricemia	0.1
Multiple sclerosis	0.1
Rheumatologic, systemic	0.1
Total	48.0%

daily doses of gabapentin in patients with and without adverse events were generally similar.

According to the prescribing physicians, 42 cases were mild (56.8%), 20 were moderate (27%), and 8 were severe (10.8%) in intensity. Four cases were not rated by the prescribing physicians. Sixty two cases (83.8%) resolved by the end of the observation period. In 58 cases (78.4%), the adverse event resolved without any changes in therapy, or resolved by reducing the dose of gabapentin.

There were two serious adverse events. One case involved a death in a patient with end stage lung cancer who was receiving gabapentin for neuropathic cancer pain. A second case involved a myocardial infarction in a patient with known pre-existing coronary artery disease. In the opinion of both prescribing physicians, neither of these adverse events was related to gabapentin use.

Patient and physician ratings for tolerability of gabapentin were similar, with more than 76% reporting very good to excellent tolerability (Figure 2).

Table 3. Concomitant medications according to indication

Medications	Percentage (N=1,214)
Oral hypoglycemics	33.0
Anti-hypertensive agents	21.2
Vitamin & nutritional supplements	19.1
Non-steroidal anti-inflammatory drugs	12.9
Analgesics, non-narcotic	10.5
Anti-platelet agents, including aspirin	9.3
Anti-convulsants	3.8
Analgesics, narcotic	3.2
Anti-depressants	3.0
Insulin	2.9
Skeletal muscle relaxants	2.4
Lipid-lowering agents	2.3
Anti-infectives, including anti-TB drugs	2.3
Central nervous system stimulants	1.8
Sedatives-hypnotics	1.5
Steroids	1.4
Anti-anginal therapy	0.9
Anti-viral agents	0.7
Anti-peptic ulcer agents	0.7
Anti-gout agents	0.6
Anti-arrhythmic agents	0.4
Immunosuppressives / anti-cancer	0.4
Anti-asthma agents	0.3
Anti-osteoporosis agents	0.3
Anesthetics (local)	0.3
Decongestants	0.2
Anti-psychotics	0.2
Sympathomimetics	0.2
Others	0.8

Efficacy of gabapentin

From 1,186 patients who responded, most patients rated their baseline pain as moderate (42.8%) or severe (41.9%) on the 10-point pain intensity scale. The mean baseline pain score for all cases using the 100mm visual analog scale was 67.8 $\pm$ 20.0 mm.

At the end of the 2-week study period, the percentage of patients who reported no pain increased to 28.6%, and 60.2% rated their pain as mild (Figure 3). The final mean visual analog scale score for all cases was 16.1 $\pm$ 15.6 mm, which was significantly lower compared to the baseline score of 67.8 $\pm$ 20.0 mm ($p < 0.05$). (Figure 4)

Patients and physicians were asked to rate their overall impression of gabapentin in terms of analgesic efficacy. Almost 70.4% of patients and 73.6% of physicians rated the efficacy of gabapentin as “very good” to “excellent” (Figure 5).

Patient status at end of study

From among the 1,214 patients who received at

Table 4A. Adverse events

Adverse events	**Percentage (N=1214)**
Dizziness, vertigo, ataxia	3.0
Drowsiness, somnolence, lightheadedness	1.9
Nausea	0.2
Fatigue	0.2
Generalized rash and allergy	0.2
Headaches, “heaviness of eyelids”	0.2
Blurred vision	0.1
Elevated blood pressure	0.1
Increase in creatinine	0.1
Myocardial infarction	0.1
Tachycardia	0.1
Death *	0.1
Total (n=74)	6.1
Patient Dropouts (reasons for withdrawals)	**Percentage (N = 1214)**
Lost to follow-up	1.5
Poor compliance / Erratic medication intake	0.7
Adverse event	0.6
Lack of efficacy	0.1
Total (n = 34)	2.9

Table 4B. Comparison of patients with adverse events according to demographics

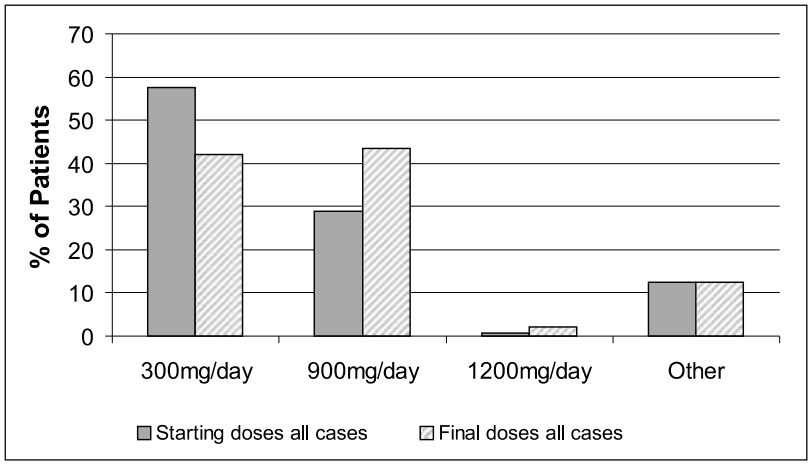
	Patients with adverse events	**Patients without adverse events**
Mean Age (years)	57 +/- 15	54 +/- 14
Male (%)	53	45
Female (%)	47	55
Mean dose (final)	646.8mg/day	611.8mg/day
Concomitant Analgesics (%)	57.5	30.6
1. Opioids	15.1	7.8
2. Non-opioids	9.1	1.6
3. NSAIDs	18.1	15.3
4. Anticonvulsants	7.5	3.7
5. Benzodiazepines	6.0	0.3
6. Antidepressants	0	0.7
7. Muscle Relaxants	1.5	1.1

* Death occurred in a patient with end stage lung cancer receiving gabapentin for neuropathic cancer pain.

least one dose of gabapentin, there were 52 patients who did not complete the minimum 2-week observation period of therapy. There were 34 documented patient dropouts (2.9%), of which only 7 (0.6%) were considered to be related to an adverse event from gabapentin (Table 4A). Withdrawals from the remaining 27 patients were due to other causes, namely, lack of efficacy (n=1 or 0.1%), loss of follow-up (n=18 or 1.5%), and poor compliance (n=8 or 0.7%). Data on dropouts was incomplete from the remaining 18 patients.

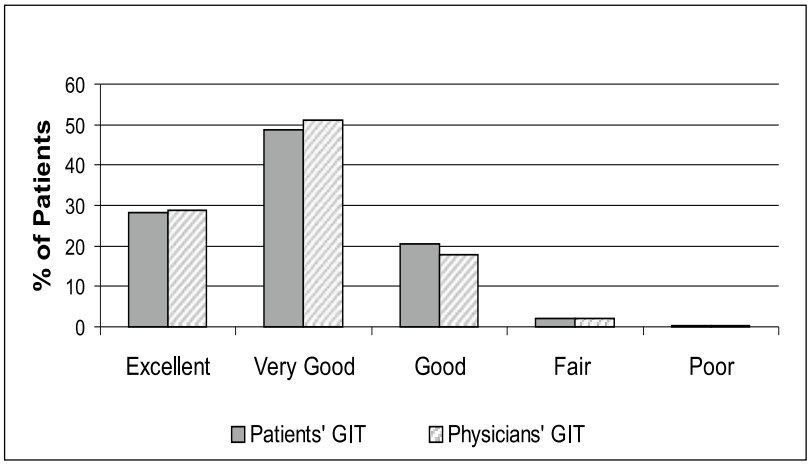
DISCUSSION

The data obtained from this post-marketing surveillance suggests that gabapentin is effective and well tolerated in Filipino patients with a variety of neuropathic pain syndromes. Although post-marketing surveillance studies are designed to detect data on safety and tolerability in normal practice settings, it is interesting to note that most patients and physicians reported analgesic efficacy at doses between 300mg to 1200mg per day. These dose requirements are generally lower compared to published case reports and series involving western populations, where doses of 900mg to 3600mg per day have been used.[8-18] It is unclear if race, genes, culture, or body mass indices account for these differences, since these factors were not controlled for in this post-marketing surveillance.



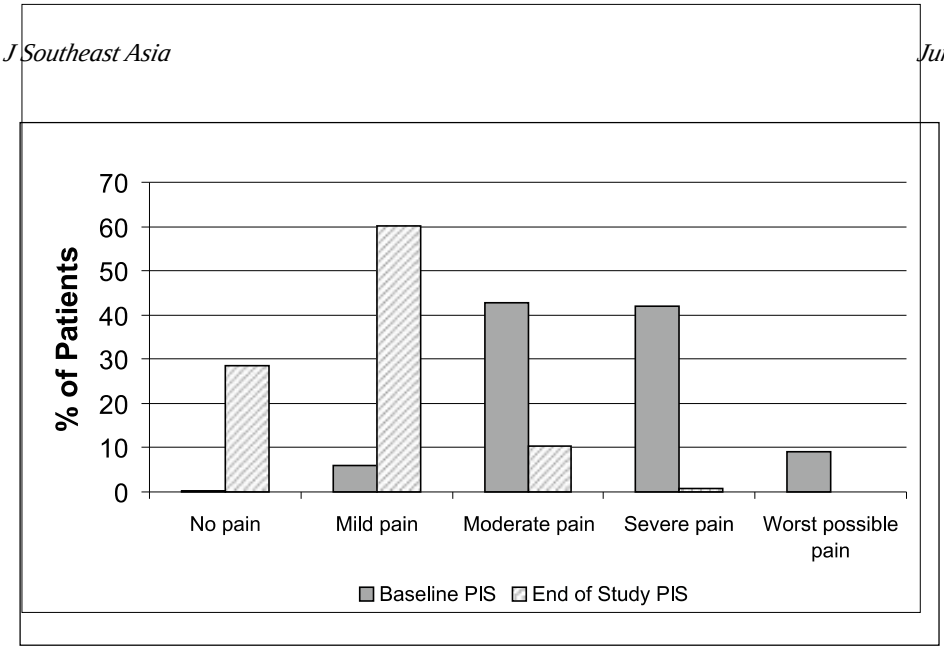
Other = either 600 mg per day (300mg BID) or > 1200mg per day

Figure 1: Starting and final doses of gabapentin (N = 1171)



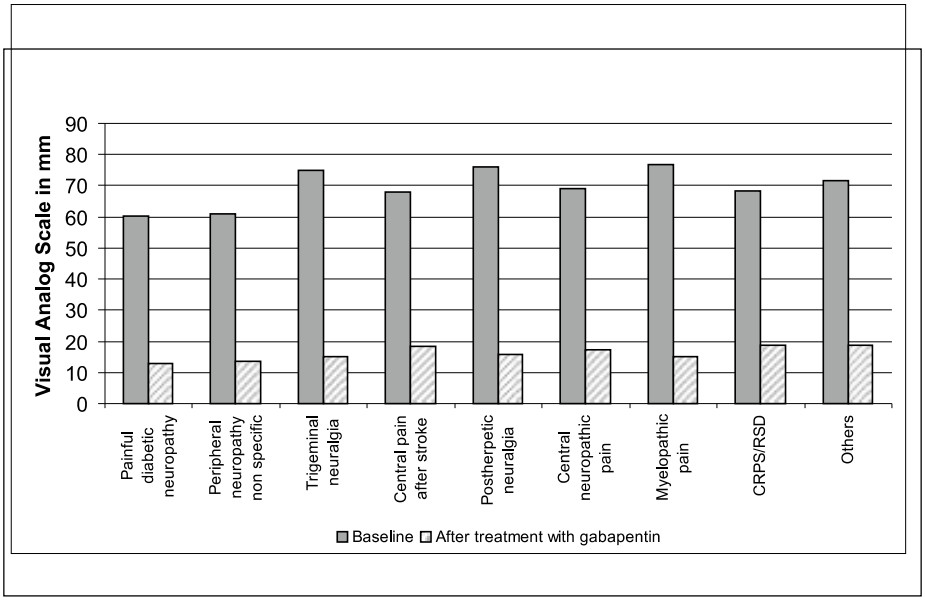
GIT = Global Impression of Tolerability

Figure 2: Patients' and physicians' Global Impression of Tolerability with gabapentin (N = 1172)



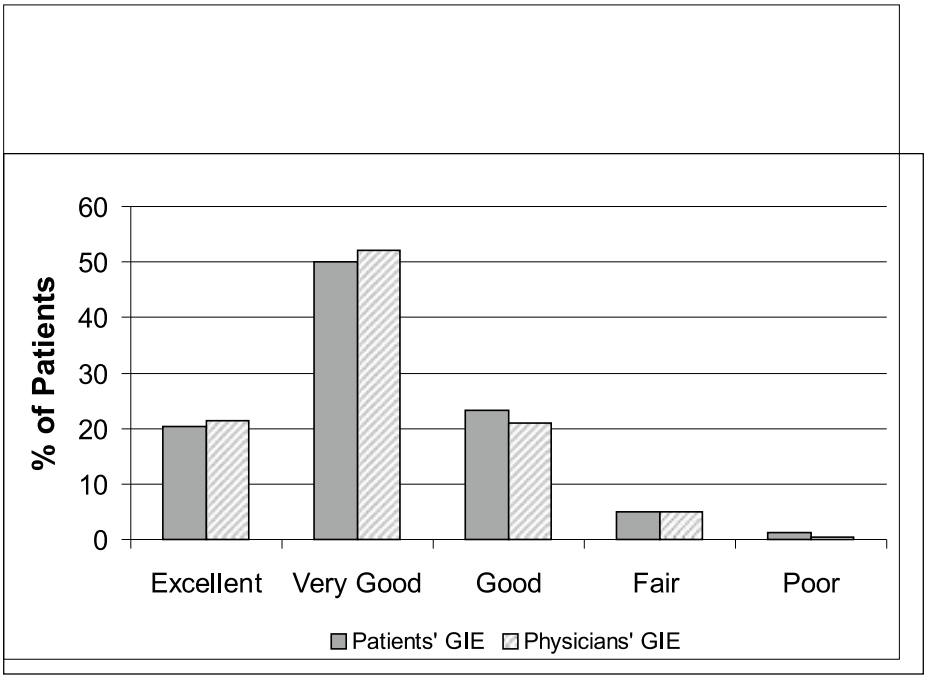
0 = no pain; 1-3 = mild pain; 4-6 = moderate pain; 7-9 = severe pain; 10 = worst possible pain
PIS = Pain Intensity Scale

Figure 3: Change in pain intensity before and after treatment (N = 1186)



p<0.5 compared to baseline for all conditions
CRPS = Complex Regional Pain Syndromes; RSD = Reflex Synpathetic Dystrophy;
"Others" includes neuropathic cancer pain, sciatica, carpal tunnel syndrome, arachnoiditis

Figure 4: Mean Visual Analog Scale scores at baseline and after treatment with gabapentin (N = 1156)



GIE = Global Impression of Efficacy

Figure 5: Patients' and physicians' Global Impression of Efficacy (N = 1195)

Although the mechanisms of action of pain relief by gabapentin remain unclear, efficacy in both open and controlled studies of neuropathic pain have been demonstrated.[19-23] In two, large, randomized and placebo-controlled trials of gabapentin in painful diabetic neuropathy and postherpetic neuralgia, doses up to 3600mg per day were shown to be effective and well-tolerated in reducing pain, as well as in improving mood, sleep and other quality of life issues.[20,22] Although this PMS showed acceptable efficacy at much lower doses, upward titration of gabapentin may be necessary if patients are initially unresponsive.[2]

Adverse events were uncommon, although duration of exposure to gabapentin may have been limited. Tolerability was rated as "very good" to "excellent," and was fairly consistent between patients and physicians. Similar to most published reports, the most commonly reported adverse events were dizziness and somnolence. In some clinical instances, somnolence may be a desirable side effect.[2] Four recent controlled trials showed that gabapentin monotherapy was efficacious in treating sleep interference in painful diabetic neuropathy and postherpetic neuralgia.[20-23]

In conclusion, gabapentin given at doses between 300 to 1200mg per day was well tolerated and associated with a low incidence of adverse events among 1214 Filipino patients with neuropathic pain. Based on quantitative and qualitative measures of efficacy, and within the limitations of a post-marketing surveillance study design, gabapentin appears to be efficacious in the management of Filipino patients with a wide variety of neuropathic pain syndromes.

ACKNOWLEDGMENTS

The authors would like to gratefully acknowledge the significant contributions of the following physicians in this post marketing surveillance study: Maritoni Abbariao, Ofelia Adapon, Ricardo Agbayani, Bernadette Aguilar, Ryndell Alava, Angelo Alcala, Mila Alquiza, Raquel Alvarez, Encarnita Ampil, Ma. Luisa Aportadera, Louella Araza, Rey Arenas, Caroline Arroyo, Rosella Autor-Padama, Alver Avestante, Richel Bacot, Jubilia Araceli Baldems, Gloria Balgomera, Glory Baltazar, Pia Banico-Villanueva, Sheila Baniqued, Emerita Barrenechea, Eril Basuil, Annette Bautista, Jeremias Bautista, Angelito Belen, Jose Beltran, Jr., Gerald Bernal, Imelda Bilocura, Noel Bilonguel, Judy Boado, Arli Bumatayo, Raquel Cadisal, Carlo Cadiz, Emerito Calderon, Fidel Caligayahan, Bernard Canlas, Corina Canlas, Robert Capatoy, Eric Capulong, Nenia May Catli, Eden Ceballo, Jean Chavez, Eleanor Chi-Ong, Arneil Chua, Alberto Cruz, Cenon Cruz, Marietta Cruz-Olaivar, Edna Cuasay, Rex David, Norman de Asis, Carl de Leon, Leewelynne de Vera, Ma. Theresa dela Serna, Elinor Delfino-Ganas, Fe delos Reyes, Marian Denopol, Carissa Dioquino, Jane Doctora, Franklin Domingo, Pura Dominguito, Gaudencio Duenas, Jr., Cecilia Dulla, Mary Warren Eduardo-Ilaga, Romeo Enriquez, Maritzie Eribal, Rosalina Espiritu, Jovy

Esteban, Guido Estorco, Bilocura Eubil, Christine Evangelista, Renato Evangelista, Grace Fernandez, Jewel Fernandez, Roy Ferrer, Ma. Belinda Fidel, Socorro Florendo, Paul Francia, Delma Franco, Mercivinia Galang, Hermenigildo Gan, Judy Anne Gatmin, Angelita Go, Manolette Guerrero, Ulysses Guevarra, Irene Igual, Werner Paul Irmsher, Francis Javier, Rustico Jimenez, Annabelle Lao, Ronnie Lao, Lyndon Laude, Ma. Arlene Lee, Deana Licup, Ana Luz Lim, Jorgen Lim, Gerard Lipana, Zenaida Lising, Johnny Lokin, Henry Lu, Corina Macalintal, Vincent Macalintal, Regina Macalintal-Canlas, Elaine Magat, May Christine Malicdan, Ma. Cecilia Mallari, Nelson Mallilin, Elma Maranon, Jovy Marcaida, Melicia Maronilla, Romil Martinez, Clifton Martirez, Dulce Mendoza, Leoneil Miranda, Margaret Modequillo, Rey Murillo, Emily Noche, Marcos Ong, Raymond Oribio, Ranulfo Orpilla, Elvis Pabua, Clive Palmares, Araceli Panelo, Jane Pasal, Ma. Daisy Pedroso, Francis Pizarro, Veronic Racho, Ma. Teresa Ramirez, Renald Ramiro, Glenford Refre, Levi Rejuso, Aprilynn Reyes, Nanette Reyes, Godfrey Robeniol, Santiago Rodriguez, Ruth Marie Roldan, Madelyn Grace Ronan, Raymond Rosales, Artemio Roxas, Jose Allen Salamatin, Marcelino Salango, Winston Salem, Chona San Gabriel, Amado San Luis, Ma. Luisa Santos, Jocelyn Sio, Anthony So, Leonor Sobrevega, Miriam Emily Soriano, Pedro Tabernero, Jr., Roberto Tabio, Jr., Ronald Talens, George Tan, Ma. Liza Tan, Yvette Tan, Edenbergh Tecson, Ernesto Tee, Elmer Tomacoer, Rolijun Torio, Wilson Tulmo, Albert Ty, Ma. Esperanza Uy, Reginita Uy, Celina Vilchez, Elsa Villagomeza, Rommel Villar, Marcelo Villarosa, Francis Jayson Villegas, Romeo Vitug, Antonio Yap, Michelli Yusay, and Jessie Yasay.

REFERENCES

1. Woolf CJ, Mannion RJ. Neuropathic pain: Aetiology, symptoms, mechanisms, and management. *Lancet* 1999; 353: 1959-64.
2. Tremont-Lukats IW, Megeff C, Bakonja MM. Anticonvulsants for neuropathic pain syndromes: Mechanisms of action and place in therapy. *Drugs* 2000; 60: 1029-52.
3. Thomas PK. Diabetic neuropathy: Mechanisms and future treatment options. *J Neurol Neurosurg Psychiatry* 1999; 67: 277-9.
4. Ashburn MA, Staats PS. Management of chronic pain. *Lancet* 1999; 353: 1865-9.
5. Karlsten R, Gordh T. How do drugs relieve neurogenic pain? *Drugs Aging* 1997; 11: 398-412.
6. Collins SL, Moore RA, McQuay HJ, Wiffen P. Antidepressants and anticonvulsants for diabetic neuropathy and postherpetic neuralgia: A quantitative systematic review. *J Pain Symptom Management* 2000; 20: 449-58.
7. Petroff OA, Rothman DL, Behar KL et al. The effect of gabapentin on brain gamma-aminobutyric acid in patients with epilepsy. *Ann Neurol* 1996; 39: 95-9.
8. Mao J, Chen LL. Gabapentin in pain management. *Anesth Analg* 2000; 91: 680-7.
9. Taylor CP. Emerging perspectives in the mechanisms of action of gabapentin. *Neurology* 1994; 44 (Suppl 5): S10-S16.
10. Rosenberg JM, Harrell C, Ristic H et al. The effect of gabapentin on neuropathic pain. *Clin J Pain* 1997; 251-5.
11. Mellick GA, Mellick LB. Gabapentin in the management of reflex sympathetic dystrophy. *J Pain Symptom Management* 1995; 10: 265-6.
12. McGraw T, Kosek P. Erythromelalgia pain managed with gabapentin. *Anesthesiology* 1997; 86: 988-990.
13. Rosner H, Rubib L, Kestenbaum A. Case report: Gabapentin adjunctive therapy in neuropathic pain states. *Clin J Pain* 1996; 2: 56-58.
14. Schachter SC, Carrazana EJ. Treatment of facial pain with gabapentin: Case reports. *J Epilepsy* 1997*;* 10: 148-149.
15. Sist T, Filadora V, Miner M, Lema M. Gabapentin for idiopathic trigeminal neuralgia: Report of two cases (letter). *Neurology* 1997; 48: 1467.
16. Valzania F, Strafella P, Nassetti SA, et al. Gabapentin in idiopathic trigeminal neuralgia (abstract). *Neurology* 1998; 50: A379.
17. Mercadante S. Gabapentin in spinal cord injury pain. *Pain Clinic* 1998; 10: 203-206.
18. Caraceni A, Zecca E, Martini C et al. Gabapentin as an adjuvant to opioid analgesia for neuropathic cancer pain. *J Pain Symptom Management* 1999; 17: 441-5.
19. Morello CM, Leckband SG, Stoner CP et al. Randomized double-blind study comparing the efficacy of gabapentin with amitryptiline on diabetic neuropathy pain. *Arch Intern Med* 1999; 159: 1931-7.
20. Backonja M, Beydoun A, Edwards KR et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus. *JAMA* 1998; 280: 1831-6.
21. Dallocchio C. Buffa C. Mazzarello P. Chiroli S. Gabapentin vs. amitriptyline in painful diabetic neuropathy: an open-label pilot study. *J Pain Symptom Management* 2000; 20: 280-5.
22. Rowbotham M, Harden N, Stacey B et al. Gabapentin for the treatment of postherpetic neuralgia: A randomized controlled trial. *JAMA* 1998; 280: 1837-42.
23. Rice AS, Maton S. Postherpetic Neuralgia Study Group. Gabapentin in postherpetic neuralgia : a randomised, double blind, placebo controlled study. *Pain* 2001 ;94 :215-24.