# Efficacy and Safety of Gabapentin as an Add-On Therapy in Refractory Partial Epileptic Patients

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**Abstract**

The study on the efficacy and safety of gabapentin as an add-on therapy trial was performed in 10 refractory partial seizure cases at Prasat Neurological Institute, Thailand from September 1996 to July 1998. This was an open-labeled titration dose of gabapentin starting at 600 mg/day add-on to the previously prescribed conventional antiepileptic drugs (AEDs). In cases that seizures could not be controlled, gabapentin dose was increased by 300 mg per day every two weeks until the total dose of 3,000 mg or until the side effects became intolerable.

The result revealed that gabapentin reduced frequency, duration and severity of seizures and also improved the patients' activities of daily living (ADL) even at the minimum dose of 600 mg. The optimal dose of gabapentin was in the range of 600 to 1,200 mg per day. Seven patients were seizure free at the end of the study. There were some precipitating factors that interfered with the efficacy of gabapentin in some patients such as stress, menstruation, fever, and alcohol intake.

Weight gain, somnolence, nystagmus, and dizziness were the major adverse events in these patients, whereas ataxia, tremor, and diplopia were found with gabapentin in a dose higher than 1,800 mg/day. These adverse events were mild and transient. No patients withdrew from the study due to adverse drug reactions. In addition, gabapentin did not alter conventional AED blood level and routine laboratory parameters.

In conclusion, gabapentin was effective and well tolerated as an add-on therapy in refractory partial epileptic Thai patients.

**Key word :** Epilepsy, Refractory Partial Seizure, Gabapentin, Partial Seizure

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Gabapentin (1(aminomethyl)-cyclohexaneacetic acid) is a gamma-aminobutyric acid (GABA) analogue. Gabapentin (Neurontin®) was approved in the United States in 1994 as an add-on drug for the treatment of refractory partial seizures. At clinically relevant concentrations *in vitro*, gabapentin does not interact with GABA, benzodiazepine, glutamate, glycine or N-methyl - D-aspartate receptors nor directly with sodium or calcium channels, however it binds with the novel site in the CNS called gabapentin binding site[1-5]. The gabapentin binding site is localized on neuronal cell bodies and is probably associated with the system L-neutral amino acid transporter.

Gabapentin has been shown to be efficacious in the treatment of refractory partial seizures and secondarily generalized tonic-clonic seizures [6-9].

Gabapentin is well tolerated[7-10]. The lack of drug-interaction potential between gabapentin and concurrent AEDs has been confirmed [8-14].

Since gabapentin is going to be launched in Thailand very soon and there are quite a number of cases of refractory partial seizure waiting for a better drug regimen, this open-labeled study of gabapentin as an add on therapy in refractory partial seizure was performed to assess its efficacy and safety in Thai patients. We have previously determined the prevalence of patients with refractory partial seizure at Prasat Neurological Institute from January 1995 to December 1996. This was found to be 3.3 cases per 1000 cases of the seizure population[15]. The patients with refractory partial seizure found in the prevalence study were recruited for this study.

## PATIENTS AND METHOD

This study was an open non-comparative dose titration.

### Definition of refractory partial seizure

Patients whose seizures could not be controlled after 4 weeks' treatment of at least two conventional AEDs e.g. phenobarbital, phenytoin. The serum levels of all conventional AEDs were in the therapeutic range and at maximal tolerable dose.

### Inclusion criteria

Patients were aged >12 years, both sexes, weight >40 kg. Refractory seizure patients had to have at least 4 attacks of simple or complex partial or secondarily generalized seizures during a period of 2 months. Patients and legal guardians needed to be able to follow the investigator's instructions. They were reliable observers, needed to be taught to be able to document the occurrence of seizures. Patients or their legal guardians needed to give written informed consent prior to starting the study.

### Exclusion criteria

Included alcohol or drug abuse in the previous year; a history of psychotic illness in the previous 6 months, patients suspected of chronic hepatic or renal diseases, patients taking concomitant medications that might lower seizure threshold, high dose amino acid, enzyme inducer and inhibitor drugs. The trial was conducted in accordance with the FDA guidelines for clinical evaluation of AEDs and in compliance with the FDA regulations pertaining to institutional review boards and informed consent.

### Study design

The trial included an 8-week baseline phase and 24-weeks treatment phase.Baseline phase was the period to observe seizure frequency before patient recruitment. During the open-labeled treatment phase, 600 mg of gabapentin was added to AEDs for two weeks and the dose was increased by 300 mg/day every two weeks until the dose of 3,000 mg/day was achieved or until the seizures were controlled. The patients who were intolerable to the adverse effects of gabapentin were withdrawn from the study. The efficacy and safety of gabapentine as an add-on therapy were evaluated every 2 weeks throughout the study.

### Evaluation of efficacy

Each patient was given a diary to record the frequency, duration time and description of each seizure. The principal efficacy variable is the response ratio (RR). This parameter compares baseline seizure frequency (B) and treatment seizure frequency (T), RR = (T-B) / (T+B), RR ranges between -1 and +1, negative value means improvement, positive value means worsening. Second variables include the per cent of patients considered as treatment responders. The term responder means 50 per cent reduction from baseline in their seizure rate, good responders mean 75 per cent reduction from baseline in their seizure rate, excellent effi-

cacy means seizure free. Other are non-responders, meaning no change of seizure rate from the baseline and worse means more seizure attacks than the baseline in their seizures. Third variable is the measurement of the severity of seizures and reported as ADL. ADL can be defined as mild (the signs and symptoms of seizure attacks do not interfere with the ADL), moderate (the signs and symptoms of seizure attacks interfere with the ADL, however patients partially maintain daily activities), severe (the signs and symptoms of seizure attacks interfere with the ADL but patients cannot maintain daily activities). Last variables are the investigator's rating of the patient's response to therapy (worse, non-response, good response and seizure free) and patients' rating of the study medication (excellent, good, fair, poor).

### Statistical analysis

Analysis was made for per cent reduction of seizure rate, per cent responder, investigator's global evaluation of improvement and patients' overall assessments of the study medication were analyzed by Wilcoxon signed rank test.

## RESULTS

The total number of out-patient screening from January 1995 to September 1995 was 3,018 cases of seizures. With strict criteria and recorrected other risk factors, there were only 10 cases with refractory partial seizures who were enrolled in this study. The demographic baseline characteristics of the ten patients assigned to add-on therapy are shown in Table 1. Following an eight-week baseline period treatment with conventional AEDs, the starting dose of 600 mg gabapentin was added to each patient. After two weeks of add-on therapy, there was 50 per cent or greater reduction in seizure frequency from baseline at the end of 600 mg add-on therapy. This reduction corresponded to the response ratio of -0.540 which was significantly lower than that of baseline ($p$=0.0078). Two patients were seizure free and maintained on 600 mg/day of gabapentin as an add-on therapy throughout the study. At the add-on dose of 900-1,800 mg/day there were other two patients whose seizures were absolutely controlled. The remainding six patients entered the dose of 2,100 mg. Among subjects who successfully completed 24 weeks study, seven patients were seizure free, and only three patients still had seizure attacks with gabapentin add-on therapy at the dose of 3,000 mg per day. The accumulated percentage of patients who were seizure free at each dose of gabapentin is illustrated in Fig. 1.

**Table 1. Patient characteristics.**

| Parameter | True refractory partial seizure patients (n = 10) |
|---|---|
| Age (yr), mean (SD) | 32.8 (8.80) |
| Sex, (%) M/F | 80/20 |
| Baseline average monthly seizure rate | |
| Mean (attack) | 15.6 |
| Median (attack) | 4.00 |
| Baseline severity of seizure (ADL) | |
| Mild | 3 |
| Moderate | 7 |
| Severe | 0 |
| Baseline seizure type (%) | |
| Simple partial | 1 |
| Complex partial | 9 |
| Duration of epilepsy mean (yr) | 4.25 (SD = 36.92) |
| Background AEDs | |
| Two AEDs | 4 |
| CBZ/VPA | 2 |
| CBZ/CNP | 2 |
| Three AEDs | 5 |
| CBZ/PHT/PHB | 3 |
| CBZ/PHB/CNP | 1 |
| PHT/VPA/CNP | 1 |
| Four AEDs | 1 |
| CBZ/PHT/VPA/CNP | 1 |

Abbreviation: CBZ, carbamazepine; PHT, phenytoin; VPA, valproate; PHB, Phenobarbital; CNP, clonazepam; [a] Rate per 28 days.

The effects of add-on gabapentin on the frequency of seizure attack are summarized in Table 2. Add-on gabapentin therapy resulted in the reduction of frequency of seizure attacks in most of the cases at every dose. Some patients experienced no change or an increase in frequency of seizure attacks. However, the number of seizure attacks was reduced in the majority of cases and in some cases whose seizure frequency remained the same. The severity of seizure attacks shifted from moderate to mild.

The severity of seizure attacks based on activities of daily living (ADL) during add-on gabapentin therapy is shown in Table 3. At the baseline period, most of the patients evaluated their ADL whether they were interfered by seizure attacks as

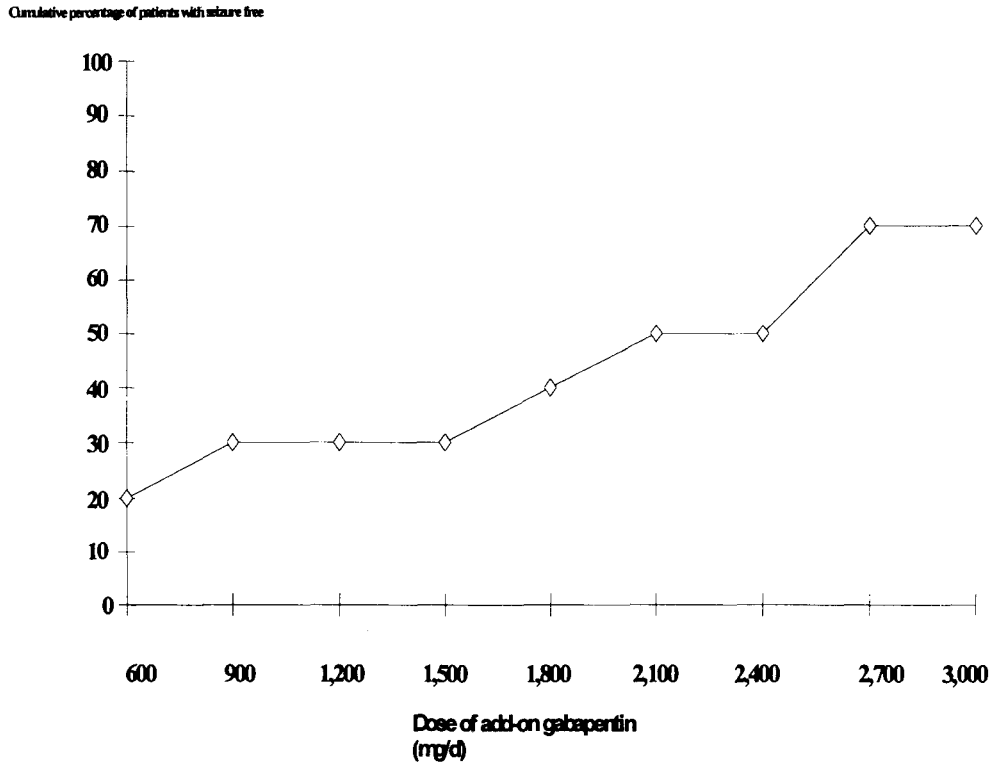


**Fig. 1. Cumulative percentage of patients with seizure free after add-on gabapentin.**

**Table 2. Reduction from baseline in average monthly seizure rate of patients completing the 24-week phase.**

| Patient status | Completion of add-on phase (n= 10) |
|---|---|
| Success (frequency) | |
| Worse | 0 |
| Non – responder | 1 |
| Responder (≥ 50% reduction) | 1 |
| Good responder (≥ 75% reduction) | 1 |
| Seizure free | 7 |
| Success (severity base on ADL) | |
| Mild | 3 |
| Moderate | - |
| Severe | - |

**Table 3. The most common adverse events during the 24-week of add-on gabapentin.**

| Body system | During 24 weeks of add-on gabapentin (n= 10) |
|---|---|
| Weight gain | 5 |
| Somnolence | 3 |
| Dizziness | 2 |
| Ataxia | 1 |
| Nystagmus | 3 |
| Tremor | 2 |
| Diplopia | 1 |

mild (3/10) and moderate (7/10). The results of these objective evaluations suggested an improved ability to perform ADL after gabapentin was added throughout the study. There were some cases in which the ADL was worsened by fever, menstruation, stress, and alcohol intake.

**Table 4. Blood levels of antiepileptic drug before and after add-on gabapentin therapy.**

| Case Number | Baseline serum level of AEDs (μg/ml) before add-on gabapentin therapy | | | | | Serum level of AEDs (μg/ml) after add-on gabapentin therapy | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | CBZ | PHT | PHB | VPA | CNP | CBZ | PHT | PHB | VPA | CNP |
| 1 | 6.08 | 12.81 | 24.96 | - | - | 6.10 | 17.00 | 17.07 | - | - |
| 2 | 9.36 | - | - | 61.46 | - | 9.21 | - | - | 63.40 | - |
| 3 | 6.93 | 16.58 | 22.26 | - | - | 5.96 | 16.13 | 19.69 | - | - |
| 4 | 8.35 | - | 20.88 | - | 0.009 | 10.23 | - | 19.66 | - | 0.009 |
| 5 | 6.88 | 14.34 | 21.34 | - | - | 8.63 | 15.93 | 19.17 | - | - |
| 6 | - | 14.32 | - | 30.18 | 0.006 | - | 13.93 | - | 33.41 | 0.006 |
| 7 | 6.22 | 15.57 | - | 70.80 | 0.006 | 6.41 | 16.13 | - | 85.07 | 0.008 |
| 8 | 7.61 | - | - | - | 0.007 | 10.53 | - | - | - | 0.006 |
| 9 | 10.99 | - | - | - | 0.013 | 11.75 | - | - | - | 0.008 |
| 10 | 10.50 | - | - | 67.80 | - | 10.23 | - | - | 65.50 | - |

Abbreviation: CBZ, carbamazepine; PHT, phenytoin; PHB, Phenobarbital; VPA, sodium valproate; CNP, clonazepam
Therapeutic blood level : CBZ = 4-12 μg/ml PHT = 10-20 μg/ml
PHB = 20-40 μg/ml VPA = 50-100 μg/ml
CNP = 0.005-0.070 μg/ml

### Adverse events

The adverse-event profile of add-on gabapentin therapy has been compiled from data obtained from 24-week periods. These adverse events are summarized in Table 3. The most common adverse events were CNS effects such as somnolence, dizziness, nystagmus, ataxia, tremor, and diplopia. High dose therapy with gabapentin (>1,800 mg/d) resulted in an increasing number of adverse events. The average onset of the first side effect of any type was two days after starting gabapentin. However, these adverse events were primarily of mild severity and generally transient in nature. Another common adverse event found in our study was weight gain. This adverse effect was sustained throughout the study. No patient withdrew from gabapentin therapy because of adverse events.

### Safety profile

Gabapentin in the dose range of 600 to 3,000 mg during the 24-week period did not lead to significant changes in routine laboratory data. These included hematological, biochemical examination and urinalysis. In addition, gabapentin did not alter serum levels of conventional antiepileptic drugs measured at the end of the study as shown in Table 4.

## DISCUSSION

Among all types of epileptic seizures, partial complex seizures are the most difficult to control[7]. About 30 per cent of patients with partial seizures remain refractory to medical management despite optimal use of conventional antiepileptic drugs[16,17]. Because of continuing difficulties in the control of partial seizures with traditional AEDs, new AED with fewer side effects and pharmacokinetic disadvantages such as gabapentin was chosen as an add-on therapy in our study. Our refractory patients were strictly screened as have been mentioned in the previous part. The efficacy of gabapentin as an add-on therapy was expressed as seizure frequency (RR ratio), duration of seizures, and ADL. RR ratio parameters had certain advantages over other measures. The distribution of values for per cent change in seizure frequency could be highly skewed. In contrast, the RR ratio was symmetrically distributed in the range of -1 to +1. Whereas, ADL measurement was the subjective data based on individual judgment.

Gabapentin has a relatively short half-life of 5 to 9 hours[13]. Consequently, the total daily dosages must be administrated in three divided doses given approximately every 8 hours. Patients were counseled to take the drug at regular intervals. Initiation with gabapentin (600 mg/d) reduced frequency, duration, and severity of seizure attacks (Wilcoxon signed rank test, $p<0.05$). The optimal dosages of gabapentin in our patients ranged from 600 to 1,200 mg daily. This optimum dosage of add-on gabapentin was rather lower than that obtained from European and USA gabapentin clinical trials in which their optimum dose ranged from

900 to 1,800 mg/d[7-9]. This was probably due to the strict criteria in recruiting the patients in our study. However, there was no apparent plateau in efficacy of gabapentin at each dose range. A higher dose from 1,800 mg per day provided even more improvement in seizure control as could be seen from the number of patients who were seizure-free, but the side effects also increased, such as somnolence.

During gabapentin treatment, some triggering factors had interfered with the efficacy of gabapentin. The triggering factors found in this study were stress, menstruation, fever, and alcoholic intake. Stressful life events have been known to increase seizure occurrence in persons with epilepsy [18]. Some stressful patients in our study had lack of rest approximately 3-5 days prior to seizure attack. Clinicians should advise patients to sleep at least 6-8 hours every night.

Fever was the most important triggering factors found in this study. Hyperthermia induces seizures in both rodents and humans[19]. There was a study which showed that hyperthermia causing a rapid increase in the concentration of glutamate (Glu) released into a cortical parenchyma before onset of seizures in rats, the increase in Glu concentration correlated with a decrease in seizure threshold[19]. Epileptic patients who have fever should be advised to take antipyretics such as paracetamol or aspirin around the clock, not the prn (as occasionally required or as needed) regimen. If the fever is rather high, the patients should be sponged down with water as soon as possible.

The seizure threshold is also decreased by alcohol[20]. In our study, some patients took alcohol approximately 3-4 hours prior to seizure attacks. It is proposed that genetic factors also play a potential role in the etiology of alcohol-associated seizure [21]. Therefore, detection of the decreased convulsant threshold and gathering knowledge about potential epileptogenic factors should become one of the goals for the treatment of epilepsy.

Concerning the adverse events and safety profile of gabapentin, all patients reported at least one adverse event. The most common adverse event found in our study was weight gain, whereas in other studies the prominent adverse event was somnolence[7-9]. Weight gain was in the range of one to five kilograms, and was not dose-related. This adverse effect persisted until the end of the study. Other adverse events found in our patients were somnolence, dizziness, and nystagmus. With a high dose of gabapentin (>1,800 mg/d), pronounced CNS effects such as tremor, ataxia, and diplopia were observed. However, these adverse events except weight gain were mild, tolerable, and transient in nature.

As expected from its pharmacokinetic properties, addition of gabapentin did not significantly alter plasma levels of other AEDs. Gabapentin is not significantly protein-bound, is not metabolized, and does not induce hepatic enzyme[2,11-13]. The result of this study was consistent with the lack of effect of gabapentin on plasma concentrations of conventional AEDs as shown in Table 4. Moreover, gabapentin did not alter any routine laboratory data especially the liver function test.

In conclusion, gabapentin has a good efficacy as an add-on therapy in the treatment of refractory partial seizures with and without secondary generalized tonic-clonic seizures. Gabapentin reduces frequency, duration of seizures, and improves ADL. Gabapentin is well tolerated and has lack of drug-interaction potential with currently used conventional AEDs. This is especially important in the treatment of epilepsy, because a significant number of patients require therapy with multiple AEDs and other drugs for coexisting conditions. Our result indicated that gabapentin was effective and well-tolerated as an add-on therapy in refractory partial epileptic Thai patients.

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# ประสิทธิภาพและความปลอดภัยของการใช้ gabapentin ในผู้ป่วยไทยที่เป็น refractory partial seizures ที่สถาบันประสาทวิทยา

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การศึกษาประสิทธิภาพของยา gabapentin ในการเป็น add-on therapy ทำในผู้ป่วย refractory partial seizure 10 คน การศึกษานี้เป็นการศึกษาแบบ open-labeled โดยเพิ่มขนาดยา gabapentin ขึ้น เริ่มที่ 600 มิลลิกรัมต่อวัน ร่วมกับยากันชักแบบเดิมที่เคยได้รับอยู่ ในกรณีที่ยังไม่สามารถควบคุมอาการชักได้ ให้เพิ่มขนาดยา gabapentin ขึ้น 300 มิลลิกรัมต่อวันทุก ๆ 2 สัปดาห์จนกระทั่งได้ขนาดยาทั้งหมด 3,000 มิลลิกรัมหรือผู้ป่วยไม่สามารถทนอาการข้างเคียงของยา ผลการศึกษานี้แสดงให้เห็นว่ายา gabapentin ลดความถี่ ระยะเวลา ความรุนแรงในการชัก และยังเพิ่มความสามารถในการดำรงชีวิตประจำวันของผู้ป่วยแม้ในขนาดยาต่ำสุดที่ 600 มิลลิกรัม ขนาดยา gabapentin ที่เหมาะสมจะอยู่ในช่วง 600-1,200 มิลลิกรัมต่อวัน ผู้ป่วย 7 คนปลอดจากการชักเมื่อจบการศึกษา ในระหว่างการใช้ยา gabapentin รักษา มีปัจจัยบางอย่างมีผลลดประสิทธิภาพของยาในผู้ป่วยบางคน เช่น ความเครียด การมีประจำเดือน ไข้ และได้รับเครื่องดื่มแอลกอฮอลล์

อาการไม่พึงประสงค์หลักที่พบในผู้ป่วยคือ น้ำหนักตัวเพิ่ม ง่วงนอน ตากระตุก และอาการวิงเวียน ส่วนอาการเดินเซ มือสั่น และเห็นภาพซ้อน จะพบในขนาดยา gabapentin มากกว่า 1,800 มิลลิกรัมต่อวัน อาการไม่พึงประสงค์ที่เกิดขึ้นมีความรุนแรงน้อยและเป็นอยู่ชั่วคราว ไม่มีผู้ป่วยถอนตัวจากการรักษาเนื่องจาก adverse event ของยา นอกจากนี้ยา gabapentin ไม่มีผลเปลี่ยนแปลงระดับยาในเลือดของยารักษาโรคลมชักแบบเดิมและไม่ทำให้เกิดความผิดปรกติกับค่าต่าง ๆ ที่ตรวจทางห้องปฏิบัติการ

สรุปได้ว่ายา gabapentin ที่ใช้เป็น add-on therapy มีประสิทธิภาพดีและผู้ป่วยทนยาได้ดีในผู้ป่วยไทยที่เป็น refractory partial seizure

**คำสำคัญ** : โรคลมชัก, ชักซนิดดื้อด้าน, กาบาเพนติน, ชักเฉพาะที่

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