# อุบัติการณ์และลักษณะทางคลินิกของอาการไม่พึงประสงค์จากยากันชักในโรงพยาบาลเชียงรายประชานุเคราะห์ ประเทศไทย
# The Incidence and Clinical Features of Anti-epileptic Drug Related Adverse Drug Reactions in Chiangrai Prachanukroh Hospital, Thailand

**นิพนธ์ต้นฉบับ** **Original Article**


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***วารสารไทยเภสัชศาสตร์และวิทยาการสุขภาพ 2563;15(3):176-182.***



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## บทคัดย่อ


**วัตถุประสงค์:** เพื่อศึกษาอุบัติการณ์และลักษณะทางคลินิกของอาการไม่พึงประสงค์จากยา (adverse drug reactions; ADRs) ในผู้ป่วยนอกที่ได้รับยากันชักเป็นครั้งแรก **วิธีการศึกษา:** เป็นการศึกษาย้อนหลัง ในผู้ป่วยนอกที่ได้รับยากันชักครั้งแรกจากโรงพยาบาลเชียงรายประชานุเคราะห์ ระหว่างวันที่ 1 กรกฎาคม 2561 ถึง 30 มิถุนายน 2562 วิเคราะห์ข้อมูลผู้ป่วยและลักษณะ ADRs โดยใช้สถิติเชิงพรรณนา เปรียบเทียบผู้ป่วยกลุ่มที่พบและไม่พบ ADRs จากยากันชัก โดย Chi-square test หรือ Fisher's exact test สำหรับตัวแปรไม่ต่อเนื่อง และ student t-test หรือ Mann-Whitney U test สำหรับตัวแปรต่อเนื่อง ตามความเหมาะสม ที่ระดับนัยสำคัญ *P*-value < 0.05 **ผลการศึกษา:** ในผู้ป่วยทั้งหมด 9,840 ราย ยากันชักที่สั่งจ่ายมากที่สุด คือ กลุ่ม non-aromatic (ใน 7,925 ราย หรือ 80.54%) มีผู้ที่ประสบ ADRs 45 ราย (0.46%) ผู้ที่มี ADRs มีอายุเฉลี่ยน้อยกว่าผู้ที่ไม่มี ADRs อย่างมีนัยสำคัญ (13.65 ± 24.78 และ 51.86 ± 18.63 ปี, ตามลำดับ, *P*-value < 0.001) พบผู้ป่วยที่ได้รับยากันชักครั้งแรกอายุ ≤ 15 ปี ในกลุ่มที่มี ADRs มากกว่ากลุ่มที่ไม่มี ADRs อย่างมีนัยสำคัญ (77.79% และ 3.60%, ตามลำดับ, *P*-value < 0.001) ไม่พบความแตกต่างระหว่างเพศ อาการผิดปกติทางผิวหนังเป็น ADRs ที่พบมากที่สุด (93.33%) โดยส่วนใหญ่พบผื่นลักษณะ maculopapular (53.33%) สาเหตุส่วนใหญ่ของ ADRs เกิดจากยา phenytoin **สรุป:** อุบัติการณ์ของ ADRs จากยากันชักเท่ากับ 0.46% อาการผิดปกติทางผิวหนังเป็นอาการไม่พึงประสงค์ที่พบมากที่สุด (93.33%) ดังนั้นควรให้คำแนะนำผู้ป่วยให้เฝ้าระวัง ADRs จากยากันชัก รวมถึงยาอื่น ๆ ที่ได้รับเป็นครั้งแรก



**คำสำคัญ:** ยากันชัก, อาการไม่พึงประสงค์จากยา, อาการผิดปกติทางผิวหนัง, ปฏิกิริยาทางผิวหนังที่รุนแรง


## Abstract


**Objective:** To determine the incidence and clinical characteristics of antiepileptic drugs (AEDs) related adverse reactions (ADRs) in out-patients who received first prescription of AEDs. **Methods**: In this retrospective cohort study, out-patients at Chiangrai Prachanukroh Hospital, Thailand receiving first prescription of antiepileptic drugs between 1 July 2018 and 30 June 2019 were evaluated. Demographic characteristics of the patients and ADRs were summarized using descriptive statistics. Differences between two groups (patients with and without ADRs) were compared using Chi-square test or Fisher's exact test for continuous variables and student t-test or Mann-Whitney U test for continuous variables, as appropriate. A two-sided *P*-value < 0.05 was considered statistically significant. **Results**: Among the 9,840 patients recruited, the most frequently prescribed drug was non-aromatic AEDs (7,925 cases or 80.54%). The incidence ADRs from AEDs was 45 in 9,840 patients (0.46%). Patients with ADRs were significantly younger than those without ADRs (13.65 ± 24.78 and 51.86 ± 18.63, respectively, *P*-value < 0.001). There were significantly more patients aged ≤ 15 years when first receiving AEDs in those with ADRs than those without ADRs (77.79% and 3.60%, respectively, *P*-value < 0.001). No significant difference regarding gender was found. Skin reactions were the most found ADR (93.33%) with maculopapular rash as the most symptom found (53.33%). Phenytoin was the most common cause of ADRs. **Conclusion:** The incidence of ADRs from AEDs was 0.46% with skin reactions as the most ADR symptoms (93.33%). Surveillance of ADRs is strongly recommended for as the safety of AEDs and all first prescription of medications.



**Keywords:** antiepileptic drugs, adverse drugs reactions, skin reactions, severe cutaneous adverse reactions



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## Introduction

Adverse drug reactions (ADRs) are a major public health concern, and play an important role in patient compliance. The symptoms of ADRs can range from mild discomfort such as drowsiness, nausea, vomiting and skin symptoms to life-threatening conditions that can cause of death.

Antiepileptic drugs (AEDs) can cause hypersensitivity reactions with a wide clinical spectrum of reactions, ranging from a mild rash to severe cutaneous reactions and death. In recent years, antiepileptic drugs (AEDs) have been increasingly used for the treatment of several non-epileptic neurological conditions and psychiatric disorders.[1-3] The prevalence of AEDs adverse drug reactions varied from 10 to more than 70%.[3] Rash is commonly a benign exanthematous eruption, which disappears within a few days after discontinuation of the drug. However, severe life threatening reactions could occur. These reactions include Stevens–

Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) characterized by focal or extensive detachment of epidermis and erosions of mucous membranes, and hypersensitivity syndrome characterized by fever, skin rash, and systemic manifestations such as hepatitis and eosinophilia. Benign rash reactions like maculopapular rash and exanthematous eruption are relatively common with aromatic AEDs (i.e., phenytoin, carbamazepine, and phenobarbital) with a frequency ranging from 5 to 15% of treated individuals.[2,3] Though hypersensitivity to AEDs is less common, the risk of severe allergy (e.g. Stevens-Johnson syndrome; SJS) is higher in AEDs.[3,4] Mortality rate of SJS, a life-threatening ADR, could be as high as 5-10%.[3]

According to the World Health Organization (WHO), pharmacovigilance also known as the “drug safety” is the science and activity relating to the detection, assessment, and prevention of adverse effect.[5] The importance of post-marketing surveillance is emphasized because ADRs cannot be fully detected during the premarketing developing process. Current trends in pharmacovigilance systems are veering towards patient involvement in the spontaneous reporting of ADRs.[5-7] Most drug allergies including AED induced allergic reactions may occur after the start of new treatment or after exposure to the first drug.

Chiangrai Prachanukroh Hospital, in the north of Thailand, had set up vigilance system since 2006 to prevent serious drug allergies in patients receiving drugs with high allergy risk for the first time. AEDs were one of the medications with such high risk of allergy. The patients were advised on how to self-monitor prodromal symptoms of severe AED allergies which could prompt them to seek urgent medical attention. In Chiangrai Prachanukroh Hospital, the patients were guided to see the pharmacist. [6] The prospective surveillance system may help serious AED allergies in patients receiving the drug for the first time. The system could also indirectly help detect more AED allergies resulting more report numbers. This study aimed to determine the incidence of ADRs and clinical characteristics of antiepileptic drugs (AEDs) related ADRs in out-patients who received first prescription of AEDs.

# Methods

In this retrospective cohort study, population was all patients of Chiangrai Prachanukroh Hospital receiving first prescription of AEDs or new users of AEDs without any specified indication. The sample was those receiving care from July 1, 2018 to June 30, 2019. The exclusion criteria were patients with insufficient data from their medical records or those who had had no clinic visits within three months after the inclusion date.

AEDs available in Chiangrai Prachanukroh Hospital were divided into 2 groups according to the structural formula namely aromatic AEDs (carbamazepine, phenytoin, phenobarbital, and lamotrigine) and non-aromatic ring AEDs (valproate, gabapentin, levetiracetam, clonazepam, and topiramate).

**Data collection procedure**

Data of participants including sex, age at first receiving AEDs, AED used, and AED allergy were collected from the Chiangrai Prachanukroh Hospital outpatient database (conventional OPD card and medical electronic program). In patients with ADR related with AED, we collected the data of clinical manifestations diagnosed by physician and time interval from the date of first receiving drug to the date of ADR occurrence (onset of ADRs).

Our surveillance system for adverse drug reaction monitoring consisted of three components. First, we had the system to identify the patients receiving first prescription of the drugs with high risk of severe skin reactions. These drugs included sulfonamides, anti-tuberculosis agents, antiretroviral, antiepileptic drugs, and antigout agents. For a given patient, if any of these drugs was prescribed for the first time, the patient was defined as the one with a high risk of drug allergy. The patient was given the alert card for drug allergy and relevant information and advice for self-monitoring. Second, we had in place the counseling service. For out-patients, they were given this service once they were defiend as at risk of drug allergy. In this counseling service, advice educational materials such as brochures about serious skin adverse reactions and symptoms of suspected ADRs were provided. Third, for every patient on drugs with high risk of hypersensitivity including AEDs, we had an intensive monitoring schedule planned out especially for the first 3 months after the start of the drug.[6] Once the patient approached the hospital with the suspected ADR, the causality of the ADR was evaluated based on the WHO-UMC criteria[8] by the clinical pharmacist and the diagnosis was made by the physician. Data of all processes were recorded in the conventional OPD chart and medical electronic database.

The diagnosis of adverse drug event was based on the diagnostic criteria proposed by the physician. For example, Stevens-Johnson syndrome (SJS) was characterized by the severe separation of the epidermis from the dermis and hemorrhagic erosions of the mucous membranes. The characteristic of toxic epidermal necrolysis (TEN) was similar to SJS but the widespread exanthema or blisters with skin detachment in TEN was > 30% of the body surface area. Drug rash and eosinophilia with systemic symptoms (DRESS) or drug hypersensitivity syndrome (DHS) was defined as (1) cutaneous drug eruption (2) adenopathy > 2 cm in diameter or hepatitis (liver transaminases > 2 times of normal) or interstitial nephritis or interstitial pneumonia or carditis, and (3) hematologic abnormalities eosinophilia. Thrombocytopenia was defined as a platelet count < $150 \times 10^3$ per µl. [9-11]

**Participant right protection**

The local Ethical Commission of Chiangrai Prachanukroh Hospital approved this study (approval number: EC CRH 025/63).

**Statistical analysis**

Demographic characteristics of the patients and characteristics of adverse drug reactions (ADR symptoms and date of ADR occurrence) were summarized using descriptive statistics (frequency with percentage and mean with standard deviation). Between the two groups (AEDs patients with and without ADRs), frequency of categorical variables including sex, age group, drug group (aromatic and non-aromatic AED), and each individual drug were compared using chi-square test or Fisher's exact, as appropriate. Differences of mean of age was compared by using student t-test (for data with normal distribution) or Mann-Whitney U test (for data with non-normal distribution), as appropriate. A two-sided *P*-value < 0.05 was considered statistically significant.

# Results

Of the 9,840 patients recruited, more female (5,459 or 55.48%) than male (4,381 or 44.52%) patients were found (Table 1). The mean age at first receiving AEDs was 51.68 ± 18.84 years. Gabapentin was the most frequently prescribed AED in this study (5,649 in 9,840 cases, or 57.41%). The most frequently prescribed drugs were non-aromatic AEDs (7,925 cases or 80.54%). The most frequently prescribed drugs in the non-aromatic AEDs in descending order were gabapentin (71.28%), clonazepam (17.51%), valproate (8.16%), levetiracetam (1.98%), and topiramate (1.06%). Aromatic AEDs were prescribed in 1,915 patients (19.46%). The most frequently prescribed aromatic AED was phenytoin (83.92%); while carbamazepine (6.37%), phenobarbital (6.06%), and lamotrigine (3.66%) were much less prescribed.

The incidence of adverse drugs reactions from AEDs was 45 in 9,840 patients (0.46%). We compared 45 patients receiving AEDs with ADRs and 9,795 patients without ADRs. There were 64.44% of female patients among those with ADRs and 55.44% amond those without ones (*P*-value 0.234).

Patients with ADRs were much younger than those without ones (13.65 ± 24.78 vs. 51.86 ± 18.63 years, respectively, *P*-value < 0.001). Consequently, there were more patients with ADRs (77.79%) than those without ADRs (3.60%) that received AEDs at age ≤ 15 years with statistical significance (*P*-value < 0.001). On the other hand, there were more patients without ADRs than those with ADRs that received AEDs at age > 15 years.

Among patients with ADRs, 84.44% of them used aromatic AEDs; while among those with no ADRs, only 19.16% of them used aromatic AEDs (*P*-value < 0.001). Once only aromatic AEDs were considered, the proportion of each drug between those with and without ADRs was statistically significant (*P*-value = 0.006). Similarly, for the non-aromatic AEDs, the proportion of each drug between those with and without ADRs was statistically significant (*P*-value < 0.001).

**Characteristics and onset of adverse drug reactions**

Phenytoin was the most common ADE causing ADR when both aromatic and non-aromatic ADEs (25 out of 45 events, or 55.56%), and only aromatic ADEs (25 out of 38 events, or 65.79%) were considered (Table 2). Valproate was the most common non-aromatic antiepileptic drug (57.14%). The onsets of AED induced ADRs varied with valproate having the longest onset (30.50 ± 16.22 days), followed by phenobarbital (19.25 ± 13.57 days), phenytoin (16.20 ± 14.53 days), lamotrigine (9.80 ± 4.97 days), and carbamazepine (4.88 ± 5.11 days) (Table 2).

Among 45 patients with AEDs induced ADRs, most of them had monotherapy AED (95.56%) (Table 3). The majority had one ADR (84.44%) while the rest 15.56% had two. Most events were skin reactions (93.33%).

**Table 1** Characteristics of the patients receiving anti-epileptic drugs (AEDs) with and without adverse drug reactions (ADRs) (N = 9,840).

| Factors | Total | | With ADRs (n = 45) | | Without ADRs (n = 9,795) | | *P*-value |
|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | |
| **Sex** | | | | | | | |
| Female | 5,459 | 55.48 | 29 | 64.44 | 5,430 | 55.44 | 0.234* |
| Male | 4,381 | 44.52 | 16 | 35.56 | 4,365 | 44.56 | |
| **Age at first receiving AEDs** (years) | | | | | | | |
| ≤15 | 388 | 3.94 | 35 | 77.79 | 353 | 3.60 | < 0.001* |
| 16 – 30 | 1,142 | 11.60 | 1 | 2.22 | 1,141 | 11.60 | 0.057* |
| 31 – 40 | 1,101 | 11.19 | 2 | 4.44 | 1,099 | 11.22 | 0.231* |
| 41 – 50 | 1,409 | 14.32 | 1 | 2.22 | 1,408 | 14.37 | 0.017* |
| 51 – 60 | 2,206 | 22.42 | 1 | 2.22 | 2,205 | 22.52 | < 0.001* |
| 61 – 70 | 2,187 | 22.23 | 3 | 6.67 | 2,184 | 22.30 | 0.011* |
| > 70 | 1,407 | 14.30 | 2 | 4.44 | 1,405 | 14.34 | 0.056 |
| Mean ± SD | 51.68 ±18.84 | | 13.65 ±24.78 | | 51.86 ±18.63 | | < 0.001** |
| **AEDs** | | | | | | | |
| Aromatic AEDs | 1,915 | 19.46 | 38 | 84.44 | 1,877 | 19.16 | < 0.001* |
| Non-aromatic AEDs | 7,925 | 80.54 | 7 | 15.56 | 7,918 | 80.84 | |
| **Aromatic AEDs** | | | | | | | |
| Carbamazepine | 122 | 6.37 | 4 | 10.53 | 118 | 6.29 | 0.006* |
| Phenytoin | 1,607 | 83.92 | 25 | 65.79 | 1,582 | 84.28 | |
| Phenobarbital | 116 | 6.06 | 4 | 10.53 | 112 | 5.97 | |
| Lamotrigine | 70 | 3.66 | 5 | 13.16 | 65 | 3.46 | |
| **Non-aromatic AEDs** | | | | | | | |
| Valproate | 647 | 8.16 | 4 | 57.14 | 643 | 8.12 | < 0.001* |
| Gabapentin | 5,649 | 71.28 | 1 | 14.29 | 5,648 | 71.33 | |
| Levetiracetam | 157 | 1.98 | 1 | 14.29 | 156 | 1.97 | |
| Clonazepam | 1,388 | 17.51 | 0 | 0 | 1,388 | 17.53 | |
| Topiramate | 84 | 1.06 | 1 | 14.29 | 83 | 1.05 | |

* Fisher's exact test.

** Mann-Whitney U test.

**Table 2** Frequencies of anti-epileptic drugs and date of onset of adverse drug reactions (N = 45 patients).

| Antiepileptic drugs | n | % within group | % overall | Onset (days), mean±SD |
|---|---|---|---|---|
| **Aromatic antiepileptic drug (n = 38)** | | | | |
| Phenytoin | 25 | 65.79 | 55.56 | 16.20 ± 14.53 |
| Lamotrigine | 5 | 13.16 | 11.11 | 9.80 ± 4.97 |
| Phenobarbital | 4 | 10.53 | 8.89 | 19.25 ± 13.57 |
| Carbamazepine | 4 | 10.53 | 8.89 | 4.88 ± 5.11 |
| **Non-aromatic antiepileptic drug (n = 7)** | | | | |
| Valproate | 4 | 57.14 | 8.89 | 30.50 ± 16.22 |
| Gabapentin | 1 | 14.29 | 2.22 | 1.00 ± 0.00 |
| Levetiracetam | 1 | 14.29 | 2.22 | 2.00 ± 0 |
| Topiramate | 1 | 14.29 | 2.22 | 5.00 ± 0 |
| Clonazepam | 0 | 0 | 0 | 0 |
| Total | 45 | | | |

**Table 3** Classification of patients using anti-epileptic drugs (AEDs) with adverse drug reactions (ADRs) (N = 45 patients).

| Classified by | N | % |
|---|---|---|
| **Number of AEDs exposed** | | |
| Monotherapy (1 AED) | 43 | 95.56 |
| Polytherapy (2 AEDs) | 2 | 4.44 |
| **Number of ADRs** | | |
| one ADR | 38 | 84.44 |
| two ADRs | 7 | 15.56 |
| **Type of ADR** | | |
| Skin reactions | 42 | 93.33 |
| Non-skin reactions | 3 | 6.67 |

The most common of ADR was maculopapular (MP) rash (24 events in 45 patients or 53.33%) which was mostly caused by phenytoin (14 out of 24 events, or 58.33%) (Table 4). Of the eight patients (17.78%) suffering from severe cutaneous adverse reactions (SCARs), 3 and 5 of them had Stevens-Johnson syndrome (SJS) and drug reaction with eosinophilia and systemic symptoms (DRESS), respectively. One of the SJS patients used combined AEDs (phenytoin and valproate). The most common AED that caused SCARs was phenytoin, followed by valproate and phenobarbital. In patients with ADRs, 3 cases (6.67%) experienced ADRs other than skin reaction. Specifically, nausea vomiting (N/V), thrombocytopenia, and amenorrhea were experienced by one patient each using gabapentin, carbamazepine and valproate, respectively. No patients experienced both skin and non-skin reactions.

**Table 4** The frequency of adverse drug reactions symptoms (N = 45 patients).

| | Itching | MP rash | Erythoderma | SJS* | DRESS* | Angioedema | Oral mucositis | Conjunc-tivitis | Thrombo-cytopenia | N/V | Amenorrhea |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Phenytoin (n = 25)† | 2 | 14 | 1 | 2‡ | 4 | 2 | 3 | 1 | | | |
| Lamotrigine (n = 5)† | | 4 | 1 | | | | | 1 | | | |
| Valproate (n = 4) | | 1 | | 1‡ | 1 | | | | | | 1 |
| Carbamazepine (n = 4)† | 1 | 1 | | | | 1 | 1 | | 1 | | |
| Phenobarbital (n = 4)† | | 2 | 1 | 1 | | | 1 | | | | |
| Gabapentin (n = 1) | | | | | | | | | | 1 | |
| Levetiracetam (n = 1) | | 1 | | | | | | | | | |
| Topiramate (n = 1) | | 1 | | | | | | | | | |
| Total (45 cases, 52 events) | 3 | 24 | 3 | 4 (3 cases) | 5 | 3 | 5 | 2 | 1 | 1 | 1 |

* Severe cutaneous adverse reactions (SCARs).

† Some patients had 2 symptoms of ADRs.

‡ Combined AEDs (of the three patient with SJS, one had phenytoin with valproate, one with phenytoin only, another one had phenobarbital only. Based on medications, there were four cases, but only three patients affected).

## Discussions and Conclusion

Our study found that the incidence of overall ADRs from AEDs (0.46% or about 4:1,000 or 45 in 9,840 AED patients) was lower than other studies.[12-14] The average rate of AED induced skin reaction fund in our study was 43 in 9,840 or 0.44%; while the overall ADR rate in southern China was 58.88% (1,807 of 3,069 patients). [12] A skin reaction to at least one AED was found in 10% of patients (10%) in Kielce, Poland.[13] A previous retrospective chart review reported an average rate of AED-associated rash of 2.8%.[14] Discrepancy between our study and others could be due to differences in

races or populations enrolled, offending drugs, and study designs.[14] For example, patients aged 18 – 90 years with epilepsy or epileptic syndromes were included in the study in Kielce, Poland[13]; while patients using AEDs regardless of indications and age were included in our study.

In accordance with previous studies, this study showed higher rates of adverse drug reactions in patients treated with aromatic AEDs compared with non-aromatic AEDs.[3,4,11,13,16] Epidemiologic and clinical analysis of drug hypersensitivity reactions (DHRs) in hospital-based series of pediatric patients from different countries showed that AEDs were frequently within the top 5 implicated drugs for the whole spectrum of clinical presentations.[14] Aromatic AEDs had 2 to 5 times higher rate of DHRs than new generation and/or nonaromatic AEDs in hospitalized and outpatient populations.[14] Aromatic ring in AEDs in can form an arene-oxide that may become immunogenic through interactions with proteins or cellular macromolecules. This hypothesis suggests that this structural commonality between AEDs may be responsible for hypersensitivity reactions. [7] Another argument supporting this hapten hypothesis is the rate of cross sensitivity that has been reported among patients using aromatic AEDs. The rate has been reported to be as high as 80%–87%.[7] In this study, phenytoin was the most frequent AED that induced ADRs (25 in 45 cases, or 56%). Some of previous studies reported phenobarbital[3] and carbamazepine.[13]

Multivariate analysis in large group of patients from UK and Europe reported no difference in ADRs between sexes. However, smaller studies and those from China and a large-scale population study in children showed that AED-related skin reactions developed significantly more often in female than male patients.[2,4,12,13] Our study found more ADRs in female than in male patients but no statistical significance (64.44% vs. 35.56%, *P*-value = 0.234).

For the factor of age, previous studies reported the frequency of rashes tended to increase with age.[13,16] However, a study reported different trend.[12] Children younger than 12 years old and adults older than 64 years old had higher risks for SCAR as reported in a study.[14] Another study reported that children younger than 5 years old had 3 to 5 times the risks for SCAR and other rash related to AEDs than other age groups.[16] Our study found the children aged 15 years or younger had a higher risk of ADRs as 77.79% of patients of this age were found among those having ADRs and 3.60% of them among those not having any (*P*-value < 0.001). On the other hand, more patients aged 16 years or older were found among those with ADRs than those without the events. Hence, mean age of patients with ADRs was much lower than those without ADRs (13.65 ± 24.78 vs. 51.86 ± 18.63 years, *P*-value < 0.001). Thus, it is important to inform the patients and closely monitor ADRs when starting AEDs to patients aged 15 years or younger.

This study showed a significant difference in frequency of each AED regarding ADRs both in aromatic and non-aromatic AEDs (*P*-value = 0.006 and < 0.001). Skin reaction was the most adverse drug reaction from AEDs in this study (42 in 45 cases, or 93.3%). The most common skin reaction was maculopapular rash (24 in 45 cases, or 53.33%) with phenytoin as the most offending drug which was consistent with a previous study reporting that MP rash was commonly associated with carbamazepine and phenytoin.[4] Eight patients with skin reactions (17.78%) suffered from severe cutaneous adverse reactions (SCARs). Three of eight patients had Stevens-Johnson Syndrome (SJS), and five patients suffered from drug reaction with eosinophilia and systemic symptoms (DRESS). Because of not controlled seizure, the physician prescribed valproate for a SJS patient currently taking phenytoin during the study period (polytherapy). The most common AED that caused SCARs was phenytoin, followed by valproate and phenobarbital. The previous study about antiepileptic drugs using Korean adverse event reporting system database showed that most adverse skin reactions associated with AEDs were benign rash or urticaria (91.8%), but severe or fatal skin reactions were not rare, occurring in up to approximately 8% of cases.[11] The common causative AEDs were lamotrigine, valproate, carbamazepine, oxcarbazepine, and levetiracetam.[11] The data from a web-based Korean SCARs registry showed that carbamazepine, lamotrigine, valproate, phenytoin, and levetiracetam were the most common culprit drugs causing SCARs in Korea.[7]

In spite of our surveillance system and special counseling in preventing serious drug allergies in patients receiving first prescriptions, we found ADRs other than skin reaction. There were a case of gabapentin-induced nausea and vomiting, a case of carbamazepine-induced thrombocytopenia, and a valproate-induced amenorrhea. These results showed that the patients were concerned with the adverse drug reaction when drugs with high risk were given. As seen in our findings, some patients had non-severe ADR symptom in addition to skin

reactions and they sought medical attention before it became more severe.

Thrombocytopenia defined as a platelet count < 150 × $10^3$ per μl[10] was the most common carbamazepine-related hematologic reaction reported to the manufacturer from 1985 to 1987, with 31 of 80 reports involving platelet abnormalities.[15] The minor decrease in platelets occurred in approximately two percent of the patients and reversed with CBZ discontinuation.[15] Our study found 1 case of carbamazepine-induced thrombocytopenia. The onset of carbamazepine-induced thrombocytopenia in this study was 5 days after receiving while the onset from previous report was 6 days to 300 days.[15] Although the mechanism of carbamazepine-induced blood dyscrasias is unknown, carbamazepine-dependent antiplatelet antibodies in a patient who developed thrombocytopenia provided support for an immune mechanism of thrombocytopenia.[15] However, it is proposed to be an allergic or toxic reaction. All AEDs have been associated with hematologic reactions. [10,15,17] Thus, it is very important to carefully monitor haematological parameters during follow-up. The patient should be educated monitor and to report signs and symptoms of possible hematologic abnormalities such as infections, fever, fatigue, ecchymosis, and bleeding through mucous membranes especially in the first year of AED therapy.[10,15,17]

Our study found 5 patients in 70 new users of lamotrigine (7.14%) suffered from skin ADRs. All of patients allergic to lamotrigine had AED monotherapy. Most of them started with lamotrigine 50 mg/day and only 1 patient started with a titration of lamotrigine 25 mg/day for 3 days then 50 mg/day before the allergic reaction occurred. The previous study also reported rash was a common side effect of lamotrigine with an incidence of 8.3%. Previous data showed the risk of a severe rash from lamotrigine was reduced by over 10 folds with slow titration schedule such as 25 mg fortnightly increments. The risk of rash is increased when lamotrigine is prescribed with valproate. Since valproate competitively inhibits lamotrigine glycoxidation in the liver, half-life of lamotrigine is increased. lamotrigine is a relatively well tolerated AED, with a wide spectrum of efficacy.[4] In some reports the frequency of the rash caused by carbamazepine and lamotrigine seems to be related to the starting dose. Both drugs are more likely to cause rashes when the initial dose is high.[4,18] Thus, it is important to start ADEs with slow titration and carefully monitor adverse drug events.[4,18]

Our study found 1 patient suffered from valproate induced amenorrhea. The mechanism for this event was the associated risk of polycystic ovarian syndrome from valproate. However, relationship between valproate, polycystic ovaries, and polycystic ovarian syndrome (menstrual irregularity and clinical evidence of hyperandrogenism) remains controversial because there are other risk factors associated with an increased risk of this syndrome such as patients with epilepsy and obesity.[19]

For the onset of ADRs, previous study showed rash onset was within days to 2 - 8 weeks, and within 2 months in some reports.[4,6,11,13] Our study showed that the mean onset of ADRs after AED initiation were 30.50 ± 16.22 days for valproate, 19.25 ± 13.57 days for phenobarbital, 16.20 ± 14.53 days for phenytoin, 9.80 ± 4.97 days for lamotrigine, and 4.88 ± 5.11 days for carbamazepine. These findings could be useful in advising patients and healthcare providers for intensive monitoring on adverse drug reactions. Prevalences of ADRs to AEDs varied according to the populations enrolled, offending drugs, and study design. Current scientific advances have found that genetic markers are useful to predict individuals susceptible to AED hypersensitivity.[14]

This study had certain limitations. The study included only new users of AEDs with all indications. A diverse array of indications could result in a vast difference in prevalence of ADRs. As a result, the number of ADR incidences could not be highly precise. Since it was a retrospective investigation on the database, we could not confirm whether the patients actually took the prescribed medications. In addition, this generalizability our findings to other parts of Thailand should be cautious since only patients and medical practice in Chiangrai were studied. Finally, other factors such as previous drug allergy and genetic factors were not studied. The outcomes and possible related factors could not fully be explained. Therefore, it is recommended that further studies incorporing a broader range of potential factors and in a larger and more diverse patient demographics should be conducted.

## References


1. Spina E, Perugi G. Antiepileptic drugs: indications other than epilepsy. Epileptic Disord 2004;6(2):57-75.
2. Wang XQ, Lang SY, Shi XB, Tian HJ, Wang RF, Yang F. Cross-reactivity of skin rashes with current antiepileptic drugs in Chinese population. Seizure. 2010;19(9):562–566.

3. Karimzadeh P, Bakrani V. Antiepileptic drug-related adverse reactions and factors influencing these reactions. *Iran J Child Neurol* 2013;7(3):25-29.
4. Fowler T, Bansal AS, Lozsádi D. Risks and management of antiepileptic drug induced skin reactions in the adult out-patient setting. *Seizure* 2019;72:61–70.
5. Wattanasombat S. Pharmacovigilance. (Accessed on Jan. 15, 2020, at https://ccpe.pharmacycouncil.org/index.php?option=article_detail&subpage=article_detail&id=393) (in Thai)
6. Wattanasombat S, Wattanasombat T, Boonsararakspong N, Sangrat P. The effectiveness of surveillance system in preventing the seriousness of drug allergies in patients recieving first prescription drugs. *Thai J Hosp Pharm* 2007;17(suppl):S39-S46. (in Thai)
7. Kim HK, Kim DY, Bae EK, Kim DW. Adverse skin reactions with antiepileptic drugs using Korea adverse event reporting system database, 2008–2017. *J Korean Med Sci* 2020;35(4):e17.
8. Suwankesawong W, Sriphiromya P, Tragulpiankit P, Phetcharat C, Sornsrivichai V. Evaluation of Thai algorithm usage for adverse drug reaction monitoring. *J Health Sci* 2016;25(4):673-82. (in Thai)
9. Pannu AK, Saroch A. Diagnostic criteria for drug rash and eosinophilia with systemic symptoms. *J Fam Med Prim Care* 2017;6(3):693–694.
10. Ali N, Auerbach HE. New-onset acute thrombocytopenia in hospitalized patients: pathophysiology and diagnostic approach. *J Commun Hosp Intern Med Perspect* 2017;7(3);157-167.
11. Park CS, Kang DY, Kang MG, et al. Severe cutaneous adverse reactions to antiepileptic drugs: a nationwide registry-based study in Korea. *Allergy Asthma Immunol Res* 2019;11(5):709-722.
12. Du Y, Lin J, Shen J, et al. Adverse drug reactions associated with six commonly used antiepileptic drugs in southern China from 2003 to 2015. *BMC Pharmacol Toxicol* 2019;20(1):7: 1-8.
13. Baszczyk B, Szpringer M, Czuczwar SJ, Lason W. Single centre 20 year survey of antiepileptic drug-induced hypersensitivity reactions. *Pharmacol Rep* 2013;65(2):399-409.
14. Ye YM, Thong BY, Park HS. Hypersensitivity to antiepileptic drugs. *Immunol Allergy Clin North Am* 2014;34(3):633-643.
15. Sobotka JL, Alexander B, Cook BL. A review of carbamazepine's hematologic reactions and monitoring recommendations. *DICP* 1990;24(12):1214-1219.
16. Kuyucu S, Caubet JC. Hypersensitivity reactions to antiepileptic drugs in children: epidemiologic, pathogenetic, clinical, and diagnostic aspects. *J Allergy Clin Immunol Pract* 2018;6(6):1879-1891.
17. Kumar R, Chivukula S, Katukuri GR, Chandrasekhar UK, Shivashankar KN. Carbamazepine induced thrombocytopenia. *J Clin Diagn Res* 2017; 11(9):OD12-OD13.
18. Feliciani C, Verrottp A, Coscione G, et al. Skin reactions due to antiepileptic drugs: several case-reports with long-term follow-up. *Int J Immunopathol Pharmacol* 2003;16(1):89-93.
19. Ayano G. Bipolar disorders and valproate: pharmacokinetics, pharmacodynamics, therapeutic effects and indications of valproate: review of articles. *Bipolar Disord* 2016;2:1-5.