Patient-reported side effects of lamotrigine during routine clinic visits

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Lamotrigine (LTG) has a more favorable side effect profile than conventional antiepileptic drugs (AEDs), and is used in patients not tolerating previous treatment.[1,2] Commonly reported side effects include skin reactions and CNS-related events.[1] Intolerable side effects, inefficacy, or both are factors that necessitate the discontinuation of an AED. In Malaysia, Lamotrigine (LTG) was first made available for general prescribing in government hospitals in 1996. Despite the availability of local data on pediatric patients, data are lacking on adult patients taking LTG as part of their treatment. Therefore, we conducted a retrospective review to look at the pattern of side effects reported by adult patients during their routine clinic visits at a teaching hospital in Malaysia. The objectives of our study were (i) to determine the incidence and types of side effects during LTG therapy, and (ii) to determine the incidence of LTG discontinuation due to side effects.

We conducted a retrospective review of medical records of patients with epilepsy attending the outpatient Neurology Clinic of Hospital Universiti Sains Malaysia (HUSM) Health Campus, Kelantan, Malaysia between January 2009 and December 2009. The review targeted adult patients (age ≥16 years old) previously or currently prescribed LTG as single or adjunctive therapy. Patients who started LTG before referral to the Neurology Clinic and those who had enrolled in LTG clinical trials were excluded from the analysis. Data were collected from the day LTG started until the last clinic visit. Data collected included patients' demographic data, age first diagnosed with epilepsy, type of epilepsy, details of LTG therapy (duration of therapy, maximum daily dose), concurrent AEDs, and any side effects reported during LTG therapy. Duration of therapy was calculated from the day LTG was started until discontinuation or last day of clinic visit. All aspects of the study protocol, including access to, and use of patient clinical information were approved by the Director, Hospital Universiti Sains Malaysia.

Statistical analysis was performed using Predictive Analytical Software (PASW) version 17 (IBM Company, Chicago, IL, USA). Patients were categorized into 2 groups; those who reported side effects and those who did not. Comparisons between groups were analyzed using independent t-test for continuous data, and Chi-square test for categorical data. Statistical significance was set at $p<0.05$.

We reviewed 106 medical records of patients who satisfied the inclusion criteria. The majority of patients (94.3%) were of the Malay ethnic group. The mean age at the time of initiation of LTG treatment was 29.5 years (range 16-72 years). The average duration of LTG therapy in these patients was 46.2 months. Seventy-one (67%) patients were taking LTG as an add-on therapy. Fifty-two patients had one concurrent AED and 19 patients had 2 concurrent AEDs. Concurrent AEDs were carbamazepine (n=30), valproic acid (n=21), levetiracetam (n=21), phenytoin (n=10), topiramate (n=6), and phenobarbitone (n=2). Fifty-nine (55.7%) patients reported a total incidence of 172 side effects while on LTG therapy. Nearly half of the incidences involved the CNS. The 5 most common side effects during LTG treatment were dizziness (n=21), headache (n=17), lethargy (n=11), drowsiness (n=10), and blurring of vision (n=9). Rash was reported in 4 patients. Drowsiness and blurring of vision were reported at around 15-18 months of therapy, which usually occurred following an increment in dose. Dizziness, headache, and lethargy were found to occur within 26-29 months after LTG was started. One patient developed an allergic reaction, presented with facial puffiness and itchiness 3 days after LTG was started.

Among patients who reported side effects (n=59), there were significantly more patients taking LTG as add-on therapy compared with those patients on monotherapy (48 versus 11; $p<0.001$). The mean duration of LTG treatment (55.3 versus 34.6 months; $p<0.001$) and maximum LTG daily dose (326.2 mg versus 273.9 mg; $p=0.03$) in the group with side effects were significantly higher than those in the group without side effects (n=47). In this cohort of patients, 18 (17%) discontinued LTG therapy; 7 were due to side effects, 7 due to lack of efficacy, and 2 due to both reasons. One patient, who had been on a combination of phenytoin and LTG became pregnant, and the doctor discontinued LTG and placed her on phenytoin only. In another patient, the doctor decided to discontinue LTG and placed him on carbamazepine only because his seizures were reported to be well controlled. The types of side effects in patients who discontinued LTG are shown in **Table 1**.

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Table 1 - Side effects reported in patients who discontinued lamotrigine (n=9). Total incidence is 14 as some patients reported more than one side effect.

Side effects	No.
Allergic reactions (facial puffiness, itchiness)	1
Rash	1
Blurred vision	1
Drowsiness	3
Muscle pain	1
Decreased appetite	2
Lethargy	3
Gastrointestinal discomfort	2
Total	**14**

Recent data from a 6-year continuation study showed that 98% of patients on LTG reported side effects.[3] Likewise, from this cohort of patients we find more than 50% reported various side effects during the course of treatment. The type and severity of side effects do not appear to differ between short-term trials and long-term studies.[3] Similar to those reported by other investigators,[1,4] side effects commonly reported in our patients involved the CNS, like dizziness, headache, and drowsiness. A higher incidence of rash has been associated with the use of higher dose, rapid titration of LTG dose, combination with valproic acid, and history of skin reaction to another AED.[5] The incidence in our patients is lower (3.8%) and is consistent with findings reported using retrospective methodologies, which is around 5%.[5]

Side effects associated with LTG therapy are more often reported during the early stage of drug exposure.[4] Our results show that common CNS side effects were reported later in therapy (15-29 months). It is possible that for some patients these side effects were present earlier but mild and tolerable, and therefore, not considered important for them to report to the doctor. However, as therapy progressed and an increase in drug dose was necessary, patients might find these side effects becoming more significant and thus, reported them to the doctor.

Previous studies have shown that patients on LTG monotherapy had better tolerability than those on add-on therapy.[2,4] Similarly, our results show that significantly more patients receiving LTG as add-on therapy reported side effects compared to those in the monotherapy group. In addition, those who reported side effects had longer duration of LTG therapy. These are characteristics consistent of patients whose seizures were not adequately controlled, but tolerated early LTG therapy, and later developed side effects at a much higher dose. This finding could partly explain why many of our patients developed CNS-related side effects since such side effects are usually dose-dependent.

Some patients in our cohort discontinued LTG due to side effects (6.6%), or due to side effect and inadequate response (1.9%). Reported discontinuation rates due to side effects vary from 5-20%.[1,3] Occurrence of rash has been cited to be the most common cause of discontinuation,[1] but this is not the case in our cohort of patients, where only one case of rash was reported.

This study has its limitations. Due to the retrospective nature of the study, it was difficult to determine whether the side effects that occurred were due to LTG or due to other AEDs concurrently taken by the patients. In routine clinical practice, reporting and assessment of side effects might be affected since neither the patient nor the doctor were masked to drug treatment. Any incidences reported or not reported depends on the ability of the patient to recall during clinic visits, which could be several months apart.

In conclusion, over half of our patients on LTG reported side effects during the course of treatment. Those taking the drug as an add-on therapy, for longer duration, and at higher doses are more likely to experience side effects. As reported elsewhere, the drug may be discontinued for inefficacy or for its side effects.

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