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Letter to the Editor

## Severe drug eruptions due to lamotrigine in Japan based on data from the relief system of the Pharmaceuticals and Medical Devices Agency

Dear Editor,

Lamotrigine (LTG) is one of the newer antiepileptic drugs (AED) and is also effective for the treatment of bipolar disorder. In Japan, LTG was first approved as add-on therapy for patients with recalcitrant epilepsy in 2008. It was approved for the suppression of recurrent/relapsed mood episodes in patients with bipolar disorder in 2011, and was also approved for monotherapy in epileptic patients in 2014. The primary safety concern with LTG is drug eruptions, with benign eruptions occurring in about 10% of patients and serious eruptions in about 0.1%.<sup>1</sup> The incidence of drug eruptions is well recognized to be dose- and titration-dependent, and is related to concomitant use of valproic acid (VPA).<sup>2</sup> Slow titration of LTG is known to markedly reduce the incidence of serious drug eruptions.<sup>3</sup> Japan has a relief system for sufferers from adverse drug reactions (ADRs) managed by the Pharmaceuticals and Medical Devices Agency (PMDA).<sup>4</sup> This system provides relief benefits for patients with diseases that require hospitalization caused by ADRs in the appropriate use of the drugs concerned. In recent years the number of cases with ADRs due to LTG assessed to determine whether or not the patients are eligible for relief benefits has increased.<sup>5</sup> We analyzed the open data on ADRs due to LTG (<http://www.pmda.go.jp/relief-services/index.html>) and elucidated the recent trend of these ADRs. The  $\chi^2$ -test was used to analyze the data, and p values of less than 0.05 were considered statistically significant.

Table 1 shows a summary of ADR cases due to LTG. The first two cases were reported in fiscal year (FY) 2009 and a total of 312 cases have been reported as of FY 2015. Figure 1(a) depicts the number of cases assessed from FY 2009 to 2015. The numbers in FY 2010 and 2011 were 8 and 9, respectively. In FY 2012, the number dramatically increased to 86, and thereafter slightly decreased to around 70, with 66, 73 and 68 cases in FY 2013, 2014 and 2015, respectively. Figure 1(b) shows the percentages of ineligible cases among the total numbers of cases assessed from FY 2009 to 2015. The percentage was 0% in FY 2009, but it increased until FY 2012, with 12.5%, 33.3% and 47.7% being ineligible in FY 2010, 2011 and 2012, respectively. Thereafter, it gradually decreased to around one-third, being 39.3%, 32.8% and 32.3% in FY 2013, 2014 and 2015, respectively. Of the 117 ineligible cases, 106 (90.6%) were judged to be so because of non-compliance with dosage and administration. Of the total of 312 patients, 92 (29.5%) were males and 220 (70.5%) were females (Table 1). Of the 312 patients, 6

(1.9%) died because of ADRs due to LTG, with 5 and 1 cases receiving and not receiving relief benefits, respectively. Of the 312 cases, LTG was the only causal drug in 228 (73.1%), whereas the other 84 (26.9%) included other causal drugs, and 19 cases (6.1%) included VPA as another causal drug. Of the 312 cases, 309 (99.0%) were drug eruptions, of which the most frequent type was erythema multiforme (32.7%), followed by drug-induced hypersensitivity syndrome (DIHS: 29.8%), the maculopapular type (13.6%), Stevens–Johnson syndrome (SJS: 10.4%) and toxic epidermal necrolysis (TEN: 6.5%, Table 1). Of the 6 fatal cases, 4 were males and 2 were females. Two cases were 80 years or older, 1 between 0 and 9, 1 between 40 and 49, 1 between 50 and 59, and 1 between 60 and 69. One case included VPA as another causal drug. Four cases were DIHS, 1 SJS, and 1 TEN.

**Table 1**  
Summary of ADR cases due to LTG.

|                |        | Eligible cases | Ineligible cases | Assessed cases |
|----------------|--------|----------------|------------------|----------------|
| Fiscal years   | 2009   | 2              | 0                | 2              |
|                | 2010   | 7              | 1                | 8              |
|                | 2011   | 6              | 3                | 9              |
|                | 2012   | 45             | 41               | 86             |
|                | 2013   | 40             | 26               | 66             |
|                | 2014   | 49             | 24               | 73             |
|                | 2015   | 46             | 22               | 68             |
|                | Total  | 195            | 117              | 312            |
| Gender         | Male   | 61             | 31               | 92 (29.5%)     |
|                | Female | 134            | 86               | 220 (70.5%)    |
|                | Total  | 195            | 117              | 312 (100.0%)   |
| Ages           | 0–9    | 2              | 0                | 2 (0.6%)       |
|                | 10–19  | 7              | 6                | 13 (4.2%)      |
|                | 20–29  | 36             | 16               | 52 (16.7%)     |
|                | 30–39  | 56             | 38               | 94 (30.1%)     |
|                | 40–49  | 41             | 24               | 65 (20.8%)     |
|                | 50–59  | 26             | 17               | 43 (13.8%)     |
|                | 60–69  | 18             | 8                | 26 (8.3%)      |
|                | 70–79  | 8              | 7                | 15 (4.8%)      |
|                | 80–    | 1              | 1                | 2 (0.6%)       |
|                | Total  | 195            | 117              | 312 (100.0%)   |
| Drug eruptions | EM     | 61 (31.6%)     | 40 (34.5%)       | 101 (32.7%)    |
|                | DIHS   | 65 (33.7%)     | 27 (23.2%)       | 92 (29.8%)     |
|                | MP     | 21 (10.9%)     | 21 (18.1%)       | 42 (13.6%)     |
|                | SJS    | 19 (9.8%)      | 13 (11.2%)       | 32 (10.4%)     |
|                | TEN    | 11 (5.7%)      | 9 (7.8%)         | 20 (6.5%)      |
|                | Others | 16 (8.3%)      | 6 (5.2%)         | 22 (7.1%)      |
|                | Total  | 193 (100.0%)   | 116 (100.0%)     | 309 (100.0%)   |

ADR, adverse drug eruption; LTG, lamotrigine; EM, erythema multiforme; DIHS, drug-induced hypersensitivity syndrome; MP, maculopapular type; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

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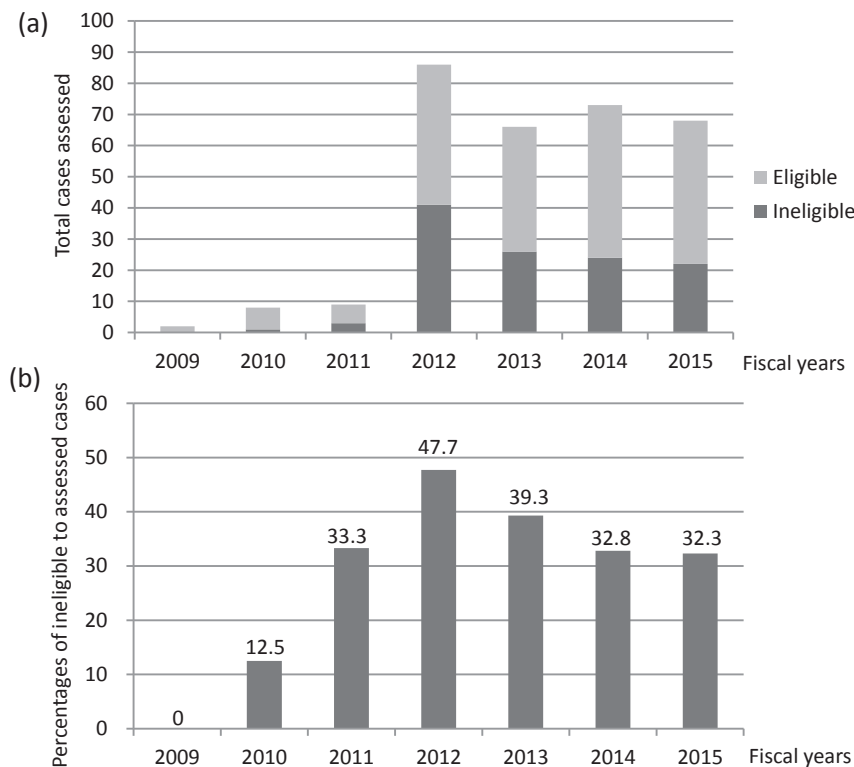


**Fig. 1.** (a) Number of assessed cases with adverse drug reactions (ADR) due to lamotrigine (LTG) from fiscal year (FY) 2009–2015. (b) Percentages of ineligible to assessed cases with ADR due to LTG from FY 2009 to 2015.

In Japan, LTG was first approved for epileptic patients in 2008, and the first ADR case due to LTG in the relief system was reported in FY 2009. The number of total cases assessed dramatically increased in FY 2012, probably because LTG was additionally approved for patients with bipolar disorder in 2011. Furthermore, the ratio of ineligible to total cases increased until FY 2012, and most of the ineligible cases were judged to be so because of non-compliance with the dosage and administration regimen. LTG must be administered with an initial dose of 25 mg/day for two weeks, followed by 50 mg/day for the next two weeks. Especially in presence of VPA, the initial dose must be 25 mg on alternate days for two weeks, followed by 25 mg/day for the next two weeks. In 2012, the PMDA sent an alert for proper use of LTG emphasizing compliance with the dosage and administration protocol and to ensure early detection of serious LTG-induced skin disorders ([http://www.info.pmda.go.jp/iyaku\\_info/tekisei\\_pmda\\_06.pdf](http://www.info.pmda.go.jp/iyaku_info/tekisei_pmda_06.pdf)).

Probably because of the alert, the ratio of ineligible to total cases has gradually decreased since FY 2013, but about one-third of cases were not eligible for relief benefits in FY 2015. In 2015, the Ministry of Health, Labour and Welfare of Japan sent the same kind of alert about the proper use of LTG, and it is expected that the ratio of ineligible to total cases will further decrease from FY 2016. About 70% of the patients were females, consistent with the observation by Wang *et al.* that there were higher rates of AED-related skin reactions in females than in males.<sup>2</sup> They also disclosed that skin reactions were reported three times as frequently with aromatic AED including LTG than with non-aromatic AED.<sup>2</sup> Based on the 6 fatal cases of this study, it seemed that the risk factors for fatality in ADRs due to LTG were gender (male), ages (younger than 10, and 80 or older) and drug eruption types (DIHS and SJS/TEN), although other large studies will be necessary.

In summary, there have been many reports of ADRs due to LTG from the relief system in the past four years and one-third of the

cases were not eligible for relief benefits in the last two years because of non-compliance with the dose and administration protocol. Psychiatrists, neurosurgeons and pediatricians should strictly comply with the guidelines for the proper use of LTG and allergologists should endeavor to ensure the early detection of severe LTG-induced skin eruptions.<sup>5</sup>

#### Conflict of interest

The authors have no conflict of interest to declare.

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