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Efficacy and Safety of Lamotrigine Monotherapy: A Review Study

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Abstract: **The main purpose of writing this review is to evaluate the efficacy and safety of lamotrigine monotherapy for treating absence seizure in paediatric population. Absence epilepsy is one of the most common childhood epilepsy syndrome account for 2-10% of seizures in children. Effective control of absence seizures is important as it increases the risk of accidental injury (head injuries and bicycle injuries) in children. (Holmes et al, 2008 and Cerminara et al, 2012)**

According to treatment guideline, ethosuximide or valproic acid is generally recommended for the first line treatment of absence seizures, however this study will assess the effectiveness of LTG as initial treatment in comparison to other conventional AEDs. This is done by analysing an open-label trial conducted with Japanese and South Korean paediatric patients and compare its result with another double-blind clinical study. The results gathered during research will be displayed graphically to show visual comparison and in tabulated form to indicate the correlation. In conclusion, the findings of the present review articles suggest that LTG monotherapy has managed to offer freedom from seizures to 35% patients suffering from absence epilepsy without generating any severe adverse effects. Hence LTG can be considered as a first-line therapy for treating absence seizure. However, this was a small-scale, uncontrolled and open label investigation hence, more research need to be done on a large scale before confirming it as an effective first-line drug. (Yasomoto et al, 2016)

Keywords: **AED Anti-epileptic drug; CAE Childhood absence epilepsy; EEG Electroencephalogram; VPA Sodium valproate; LTG Lamotrigine.**

1. INTRODUCTION

Childhood absence epilepsy is one of the most common form of paediatric epilepsy accounting for ~17% of all epilepsy cases in children. It is usually characterised by 3Hz SWD accompanied by multiple absence seizures. This review has mainly evaluated the findings of an open-label trial with 20 participants between 4-12 years of age with minimum 7kg weight. Each of the patients have absence seizure characterised by the 3Hz spike-and-wave EEG activity. The exclusion criteria include children diagnosed with partial or generalised seizures other than typical absence seizure, those with history of rash associated with other treatments, children on medication for psychiatric disorder, hyperactivity disorder or attention deficit disorder were excluded from this study. Additionally, patients who required hospitalisation for severe psychiatric condition in the past were excluded as well.

2. METHOD

A literature search for publications were performed until September 2016 including databases such as MEDLINE, pubmed, Science direct and etc in order to search an original research or report in which paediatric patients are receiving LTG doses with safety and efficacy as an outcome measure. Key articles were identified and further research was done by identifying relevant references from the individual articles. Additionally, key terms were searched such as lamotrigine, absence epilepsy, EEG, pharmacology of LTG and even combining lamotrigine with paediatric epilepsy was carried out.

3. RESULT

Twenty patients from Japanese (16) and South Korean (4) background entered in this trial. the trial is composed of different phases. 20 participants entered into fixed escalation phase and was administered 0.3 mg/kg/day for first two weeks and then 0.6 mg/kg/day for following two weeks. During which 3 participants achieved seizure-free status as only 17 participants received incremented LTG dosage at each visit during escalation phase.

Figure 1 shows the number of patients who had received different incremented dosage of LTG at each visit. It demonstrates that at each visit dosage was increased by 0.6mg/kg/day up to 9.6 mg/kg/day slightly lower than the maximum tolerable LTG dose. The number of patients receiving LTG at each visit during this phase is also gradually decreasing (at 9.6 mg/kg/day only one patient received LTG) as patients are becoming seizure-free.

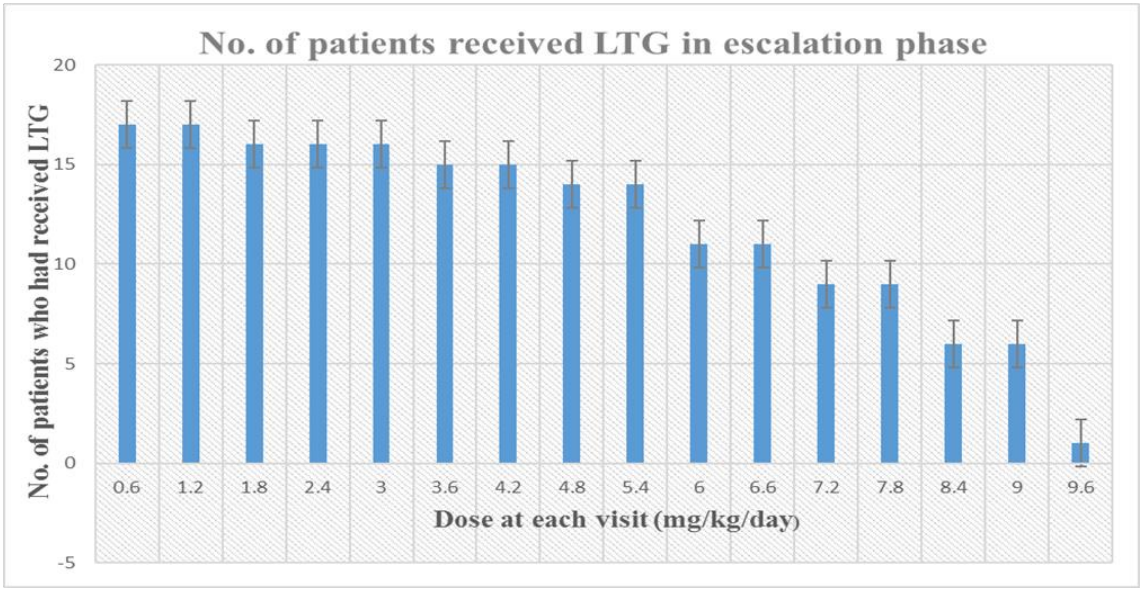

Figure 1: No. of patients received LTG in escalation phase

Figure 2 shows the numbers of seizure free patients at each visit with incremented doses during escalation phase confirmed by HV-clinical signs. At 4.8 mg/kg/day maximum (4) number of patients become seizure whereas at 4.2, 6.6 and 7.8 mg/kg/day no patients become seizure free although figure 1.9 shows at 4.2 ,6.6 and 7.8 mg/kg/day around 15, 11 and 9 patients received LTG respectively.

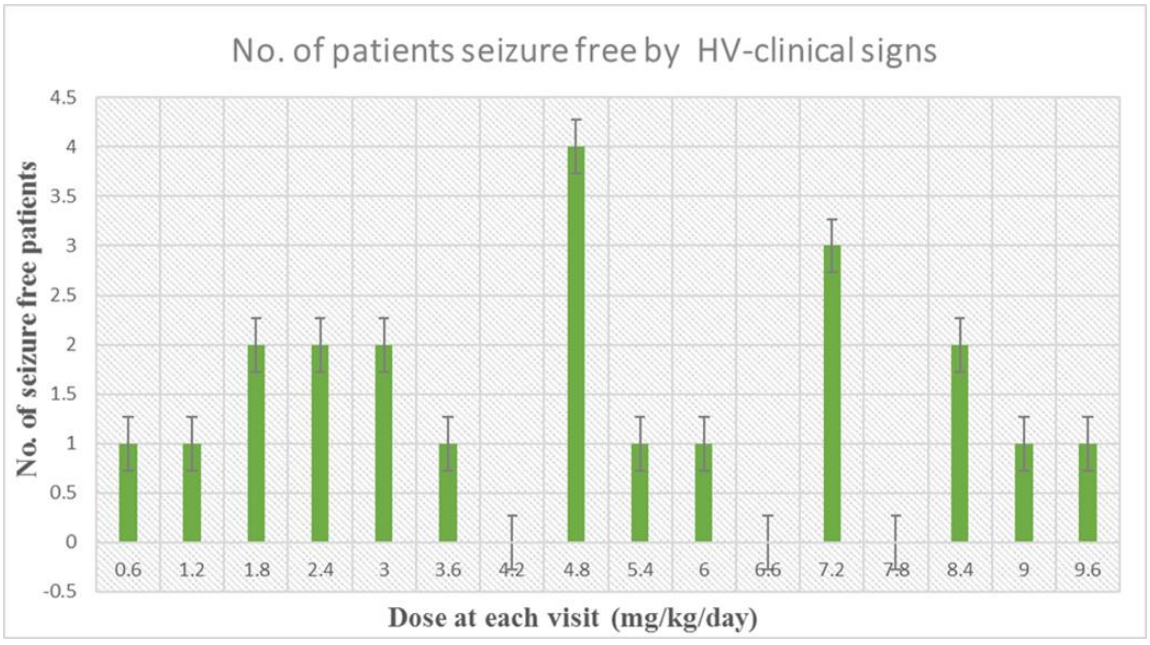

Figure 2: No. of seizure-free patients

Figure 2.1 represent the overall seizure free rate during the escalation phase. It reveals that at highest tolerable dose (9.6 mg/kg/day) 100% patients were seizure-free as the two above graphs shows that at this dose 1 patient received LTG and 1 patient become seizure free. Although at 4.8 mg/kg/day maximum rise in seizure-free patients number can be seen (graph 2) but 14 patients received LTG (Graph 1) and only 4 of them become seizure-free hence the seizure-free rate falls down to 28.6 %.

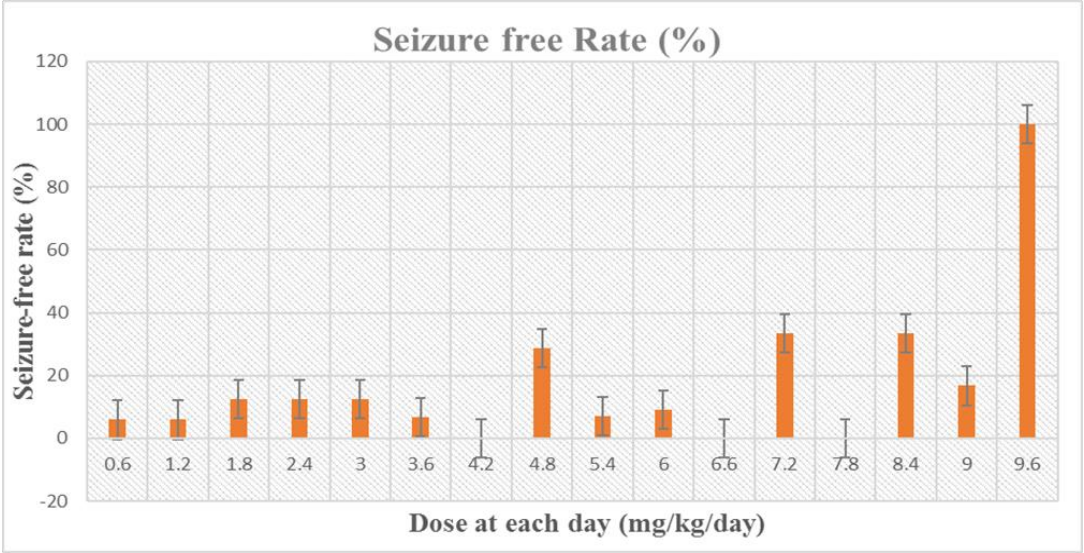

Figure 2.1: Seizure-free rate

The chart below (figure 2.2) shows the flow of the trial and highlight the important findings of the experiment. It reveals that 35% (7/20) patients are seizure-free at the end of the maintenance phase confirmed by HV-EEG and most patients who stayed seizure-free during escalation phase had managed to maintain seizure-free status during 12-week maintenance and 12-week extension phase. Primary and secondary endpoints are also pointed at the chart below which is critical while considering the efficacy of the LTG. Most patients withdrawn from the trial due to the adverse events which are shown in the figure 2.3.

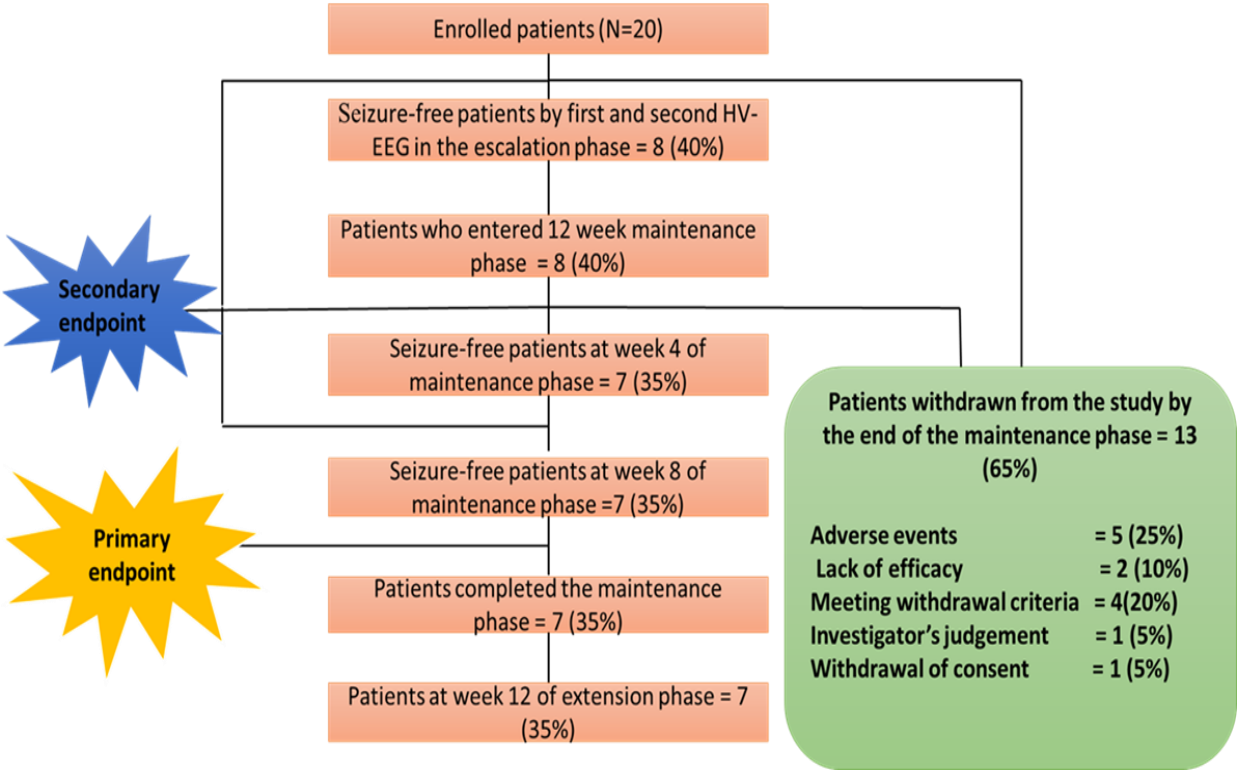

Figure 2.2 Summary of the trial

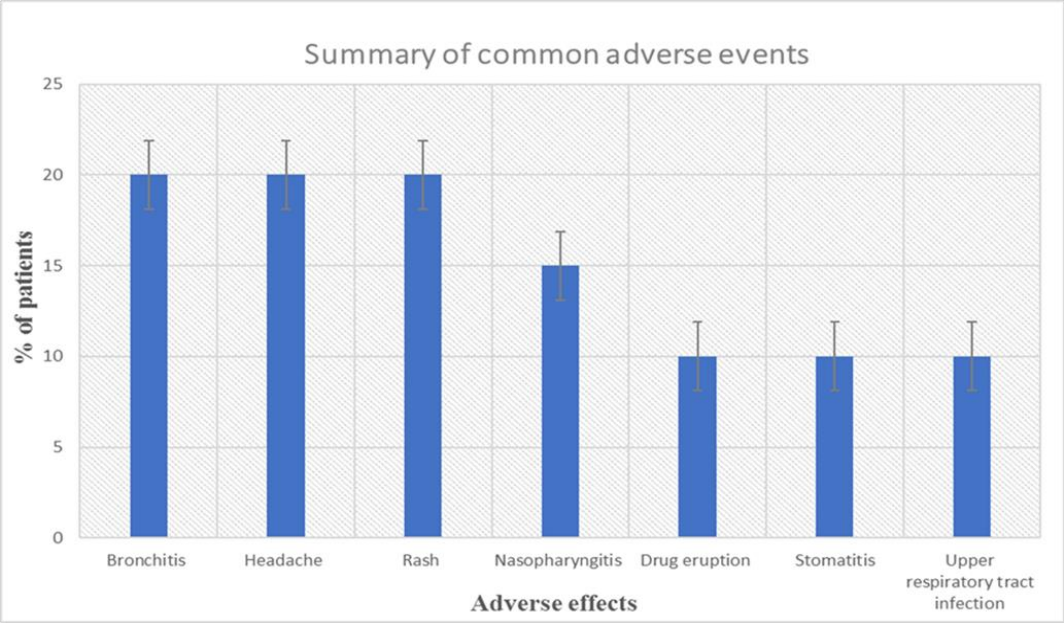

Figure 2.3: Summary of adverse events

4. DISCUSSION

Based on the report of the previous clinical trial (responder enriched design) of LTG monotherapy, it was pre-assumed that 44% patients will be seizure-free at the primary endpoint of this study. However, the present study suggest that 35% patients stayed seizure-free at the end of maintenance phase (primary endpoint) which is comparatively lower than the pre-trial hypothesis. This is because in the previous double blind study, LTG responded participants were randomised into placebo group with tapered LTG doses and group with extended LTG treatment during the 4-weeks placebo-controlled phase. Statistically more seizure-free patients were found in the LTG group (62%) as compared to placebo group (20%) shown in the graph below. (Frank et al, 1999) But in another trial of participants between 3-10 years, 55.5% patients responded to LTG therapy which is also lower than the Frank's set hypothesis. This might be due to difference in age range, as Frank's trial include participants between 3-15 years of age. (Coppola et al, 2004)

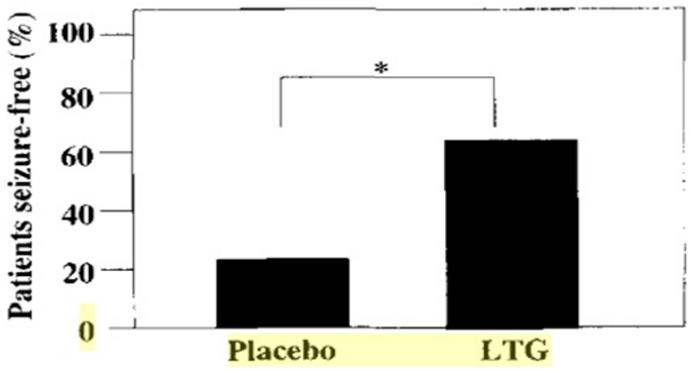

Figure 2.4: Seizure-free patients. (Frank et al, 1999)

Based on these figures, the factual seizure-free rate of placebo group in any clinical study was assumed to be 20% on which the present open-label study was based. Seizure-free rate of the present study (35%) is higher than the placebo group in the previous group. In fact, in the current trial majority of responding patients entered into the maintenance phase and continued until 12-week of extension phase, particularly during this period, 85.7% patients become seizure-free with mean 0.06 days/week of seizure episodes. Hence, LTG monotherapy seems to be effective in treating absence seizures in children. Upon tampering LTG to placebo in the previous study, seizure-free rate decreases which indicates reoccurrence of seizure soon after LTG cessation whereas patients remain seizure in the present study during extension phase suggesting effectivity of LTG therapy. (Yasumoto et al, 2016)

Present study indicates that the effective LTG dose lies between 0.6-9.6 mg/kg/day during escalation phase with mean daily dose of 6.5 mg/kg/day during maintenance phase similar for both Japanese and Korean patients, which completely overlapped with the effective dose reported by Frank and colleagues in pre-trial hypothesis. Though, some patients achieved freedom from seizure below this dose as well during first 2-weeks of fixed escalation phase. (Coppola et al,2004 and Yasumoto et al, 2016) Another research suggest that LTG plasma concentration in patients who were not seizure free is two times higher than patients who achieved freedom from seizure, suggesting that there is no association between response rate and the LTG plasma concentration. (Holmes et al, 2008)

This study presents similar adverse events to previous double-blind trial excluding rash. In this study, 20% patients exhibit rashes among which 10% are drug-related resulted in withdrawal from study and 10% are not drug-related hence are not withdrawn. Skin rashes is one of the common side-effects associated with LTG therapy and often result in treatment discontinuation. Nowadays, rash incidence is considered as dose- and titration-dependent, hence upon introduction of 'gradual titration schedule' and low starting dosages, LTG related skin reactions has reduced from 1 to 0.01%. However, past history of such reactions with other AEDs and age below 13 years are identified as equivalent risk factor for developing rashes. (Błaszczyk et al,2015 and Wang et al, 2015) It is also notified that the risk of developing rashes is higher in case of combination therapy with VPA whereas co-medication with enzyme-inducing antiepileptic drugs reduces the risk. (Wang et al, 2010) None of the other adverse effects in the present study are considered to be drug-related hence patients are not withdrawn from the study

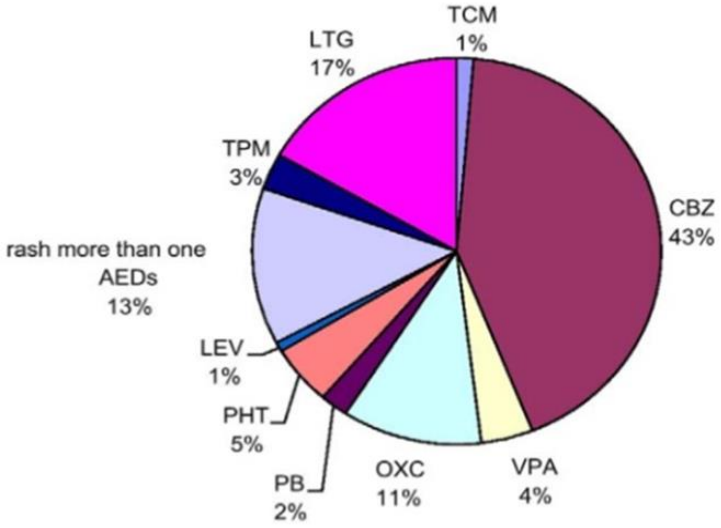

Figure 2.5: Drugs causing skin rash (Wang et al, 2010)

Lamotrigine principally act at voltage-dependent sodium channel and block their conductance in order to block glutamate release by inhibiting depolarization of the glutaminergic presynaptic membrane. Unlike other sodium channel blockers such as carbamazepine it has a wide spectrum of action and recently it demonstrates its effect on HCN channel which could explain its efficacy in absence epilepsy. (Nakatani et al, 2013 and Kase et al, 2011) There are four HCN channel subtypes encoded by HCN1-4 gene. Deletion of triple proline in HCN2 gene, alters the HCN2 subunit in thalamus resulting in fire bursts of action potential leading to spontaneous absence seizure characterised by 5Hz SWD. Lamotrigine blocks the rhythmic action potential firing as a result of increasing Ih by approximately 10mv depolarising shift leading to gain of function. (Poolos, 2012 and Reid et al,2011)

Valproate and ethosuximide are generally recommended as a first-line therapy for AS and are known to be equally effective. However, valproate is often associated with weight gain and is not recommendable for women of childbearing age and recently result in fetal abnormalities during pregnancies. Hence LTG is being considered as a fist line drug and several comparative studies have been conducted. (Posner et al, 2005) A double-blind study with 38 newly diagnosed AS patients suggested that LTG is less effective than VPA. Similarly, another randomised trial with 453 participants reported that VPA and ESM is more effective than LTG however ESM and LTG is better tolerated than VPA possibly due to weight gain as 8 patients were withdrawn from this trial for gain in weight and also LTG and ESM are known to cause less attention dysfunction than VPA. (Vrielynck, 2013) Also conducted a small scale study comparing LTG and VPA efficacy, in which both the drugs showed similar seizure-free rates after 12 months of treatment. (2004)

5. CONCLUSION

Thus, after analysing result of the present open-label study and considering the following previous studies, it can be concluded that LTG monotherapy is effective in treating untreated or newly-diagnosed typical absence seizures in children. Although ESM is considered as a best initial monotherapy but it seems even the best treatment fails in 55% of children so improvement and alternate treatment options including LTG and VPA are required. However, the present study is uncontrolled, open label and comparatively small-scale hence might not provide sufficient data for assessing the efficacy and safety of LTG. Therefore, more research and large scale trial is required for better comparison. (Yasomoto et al, 2016)

REFERENCES

[1] Blaszczyk, B., Lason, W. and Czuczwar, S. J. (2015) 'Antiepileptic drugs and adverse skin reactions: An update', Pharmacological Reports, 67(3), pp. 426-434.

[2] Cerminara, C., Coniglio, A., El-Malhany, N., Casarelli, L. and Curatolo, P. (2012) 'Two epileptic syndromes, one brain: Childhood absence epilepsy and benign childhood epilepsy with centrotemporal spikes', Seizure-European Journal of Epilepsy, 21(1), pp. 70-74.

[3] Coppola, G., Besag, F., Cusmai, R., Dulac, O., Kluger, G., Moavero, R., Nabbout, R., Nikanorova, M., Pisani, F., Verrotti, A., von Stuelpnagel, C. and Curatolo, P. (2014) 'Current role of rufinamide in the treatment of childhood epilepsy: Literature review and treatment guidelines', European Journal of Paediatric Neurology, 18(6), pp. 685-690.

[4] Coppola, G., Licciardi, F., Sciscio, N., Russo, F., Carotenuto, M. and Pascotto, A. (2004) 'Lamotrigine as first-line drug in childhood absence epilepsy: a clinical and neurophysiological study', Brain & Development, 26(1), pp. 26-29.

[5] Frank, L. M., Enlow, T., Holmes, G. L., Manasco, P., Concannon, S., Chen, C., Womble, G. and Casale, E. J. (1999) 'Lamictal (lamotrigine) monotherapy for typical absence seizures in children', Epilepsia, 40(7), pp. 973-979.

[6] Holmes, G. L., Frank, L. M., Sheth, R. D., Philbrook, B., Wooten, J. D., Vuong, A., Kerls, S., Hammer, A. E. and Messenheimer, J. (2008) 'Lamotrigine monotherapy for newly diagnosed typical absence seizures in children', Epilepsy Research, 82(2-3), pp. 124-132.

[7] Kase, D., Inoue, T. and Imoto, K. (2012) 'Roles of the subthalamic nucleus and subthalamic HCN channels in absence seizures', Journal of Neurophysiology, 107(1), pp. 393-406.

[8] Nirmal, S. and Hutchinson, R. (2013) 'When and how should we treat epilepsy in children?',

[9] Poolos, N. P. (2010) 'HCN channelopathy in epilepsy', Epilepsia, 51, pp. 12-12.

[10] Vrielynck, P. (2013) 'Current and emerging treatments for absence seizures in young patients', Neuropsychiatric Disease and Treatment, 9, pp. 963-974.

[11] Wang, X.-q., Lang, S.-y., Shi, X.-b., Tian, H.-j., Wang, R.-f. and Yang, F. (2010) 'Cross-reactivity of skin rashes with current antiepileptic drugs in Chinese population', Seizure-European Journal of Epilepsy, 19(9), pp. 562-566.

[12] Wang, X.-q., Xiong, J., Xu, W.-H., Yu, S.-y., Huang, X.-s., Zhang, J.-t., Tian, C.-l., Huang, D.-h., Jia, W.-q. and Lang, S.-y. (2015) 'Risk of a lamotrigine-related skin rash: Current meta-analysis and postmarketing cohort analysis', Seizure-European Journal of Epilepsy, 25, pp. 52-61.

[13] Yasumoto, S., Shimizu, M., Sato, K., Kurata, A. and Numachi, Y. (2016) 'Lamotrigine monotherapy for newly diagnosed typical absence seizures in children: A multi-center, uncontrolled, open-label study', Brain & development, 38(4), pp. 407-13.