PEER REVIEW HISTORY

BMJ Paediatrics Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Retrospective review of paediatric cases reports of Stevens-Johnson syndrome and toxic epidermal necrolysis with lamotrigine from an international pharmacovigilance database
AUTHORS	Egunsola, Oluwaseun; Star, Kristina; Juhlin, Kristina; Kardaun, Sylvia; Choonara, Imti; Sammons, Helen

VERSION 1 - REVIEW

REVIEWER	Ferrandiz-Pulido, C. Hospital Universitari Vall d'Hebron, Barcelona, Spain Competing interests: None declared
REVIEW RETURNED	01-May-2017

GENERAL COMMENTS	This is a interesting study of risk factors associated to the development of SJS/TEN with regard to lamotrigine exposure. Methodology is based on a database where cases are included from doctors/pharmacologists...from 40 different countries. This kind of database are useful because of high number of patients, but often offer limitations because of heterogeneity of data. However, these limitations are reflected in the manuscript. The title should better reflect the aim of the study: Should specify the population of study (paediatric) and also diseases studied (SJS and toxic epidermal necrolysis). In the abstract is used the acronim "VPA", which should be completely written (valproic acid), at least first time. Moreover, int the design paragraph should be added: "Reported time from LTG start to SJS/TEN onset, indication for use, and dose was explored, AND CONCOMITANT DRUGS." - Introduction: adequate. - Method: adequate - Results: it is not clear to me the following sentence: "LTG was co-reported with VPA in 207 (207/486, 43%) of the SJS/TEN cases and administered alone in 158 of the SJS/TEN cases (158/486, 33%). "And the other 21%? Discussion is adequately based on results of the study. Conclusion are appropiate.

REVIEWER	Mockenhaupt, Maja Medical Center - University of Freiburg Competing interests: no
REVIEW RETURNED	06-Jun-2017

GENERAL COMMENTS	The authors have addressed an interesting topic. However, I have the following comments: 1. The incidence of Stevens-Johnson syndrome (SJS) and

	toxic epidermal necrolysis (TEN) reported here is based on old non-original publications, which either refer to retrospective studies performed in the 1980s or data-base reviews of the same period without thorough clinical case validation. Therefore, I suggest to quote prospectively ascertained data of validated cases as those published by a population-based registry (Rzany B et al, 1996). 2. Mortality rates do vary considerably, but the main factors are disease severity (based on skin detachment) and age of the patient reflecting also underlying conditions. Due to severity, patients are treated in different hospital units, e.g. less severe cases in departments or dermatology or paediatrics, more severe cases in intensive care or burn units. Thus, the major factor of varying mortality is not the unit of treatment per se and the experience of the treating physicians, but rather disease severity by itself. 3. It may be true that “a history of previous AED-related rash and age younger than 13 years are the greatest risk factors of developing lamotrigine (LTG) rash”, but this does not account for SJS/TEN. In the studies on drug risks for SJS/TEN that the authors quote, previous adverse reactions were not significantly more frequent in cases (i.e. patients with SJS/TEN) than in controls. Therefore, this sentence is confusing and should be omitted. 4. There is no description on how or whether at all the diagnosis was validated. The population-based registry mentioned before showed that approx. half of the cases reported as SJS/TEN proved to be no cases after standardized review blinded for exposures. Do the authors really believe that the rate of false diagnoses is lower in their compilation of spontaneous reports? I strongly doubt this. 5. Since in a number of years following the approval of LTG in Europe it was administered as an add-on drug, it is no surprise that many patients received treatment of LTG and valproic acid (VPA) in parallel. However, the case-control study the authors quote as ref. 4 could demonstrate that the risk is confined to LTG and not to VPA. If the authors want to show a risk for VPA, they should look at the SJS/TEN-cases attributed to VPA w/o LTG-use and investigate the time latency between beginning of drug use and onset of the adverse reaction. If their cases are truly SJS/TEN and not erythema multiforme (EM), they will find a completely different pattern. Therefore, the conclusion that the risk to develop SJS/TEN is higher when LTG and VPA are used concomitantly than LTG alone is wrong. Pharmacologic investigations, however, have shown that the half-life of LTG is longer when taken together with VPA. Therefore, it was advised that VPA should be stopped as well when a patient developed SJS/TEN after the use of LTG, but can be re-administered when the skin has healed. But this is a different topic. 6. According to treatment guidelines, It is obvious that carbamazepine and phenobarbital are less likely to be combined with VPA than LTG. Therefore, this analysis as well as table 2 is misleading and should be omitted. 7. The fact that SJS/TEN occurred within 8 weeks after beginning of drug use was shown in two different European studies, as references 4 and 5 show (not only in one, as stated in the manuscript; ref.5). Thus, statement a) under the headline “What this study adds” is not correct. 8. The second statement under this heading is incorrect as well or at least there is no proof at all that the statement “VPA and LTG comedication increases the risk of SJS/TEN” is true. 9. The limitations of the study have been described, but in addition, it should be stated that not only cases of EM may have

	been misdiagnosed as SJS/TEN, but also cases of other cutaneous conditions including maculopapular exanthems etc. 10. Despite the limitations and pitfalls related to the analysis of spontaneous reports data, which were rather collected to identify alerts than to perform pharmaco-epidemiologic analyses, this study has a lot of confirmatory potential. With a higher number of exposed but clinically not validated cases it is actually able to confirm the results of earlier case-control studies in the field, which were based on lower numbers of strictly validated cases with detailed data on drug exposure. In my opinion, this is the real value of using the approach the authors have chosen.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Comment 1

The title should better reflect the aim of the study: Should specify the population of study (paediatric) and also diseases studied (SJS and toxic epidermal necrolysis).

Reply

The title has been modified

Comment 2

In the abstract is used the acronim "VPA", which should be completely written (valproic acid), at least first time. Moreover, int the design paragraph should be added: "Reported time from LTG start to SJS/TEN onset, indication for use, and dose was explored, AND CONCOMITANT DRUGS."

Reply

The abbreviation has been fully written. Evaluation of co-reported (concomitant) drugs was mentioned in parenthesis in the next sentence.

Comment 3

Results: it is not clear to me the following sentence: "LTG was co-reported with VPA in 207 (207/486, 43%) of the SJS/TEN cases and administered alone in 158 of the SJS/TEN cases (158/486, 33%). "And the other 21%?

Reply

The sentence has been clarified.

Reviewer 2

Comment 1

The incidence of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) reported here is based on old non-original publications, which either refer to retrospective studies performed in the 1980s or data-base reviews of the same period without thorough clinical case validation. Therefore, I suggest to quote prospectively ascertained data of validated cases as those published by a population-based registry (Rzany B et al, 1996).

Reply

The incidence has been modified and suggested reference added.

Comment 2.

Mortality rates do vary considerably, but the main factors are disease severity (based on skin detachment) and age of the patient reflecting also underlying conditions. Due to severity, patients are treated in different hospital units, e.g. less severe cases in departments or dermatology or paediatrics, more severe cases in intensive care or burn units. Thus, the major factor of varying mortality is not the unit of treatment per se and the experience of the treating physicians, but rather disease severity by itself.

Reply

The sentence has been deleted

Comment 3.

It may be true that “a history of previous AED-related rash and age younger than 13 years are the greatest risk factors of developing lamotrigine (LTG) rash”, but this does not account for SJS/TEN. In the studies on drug risks for SJS/TEN that the authors quote, previous adverse reactions were not significantly more frequent in cases (i.e. patients with SJS/TEN) than in controls. Therefore, this sentence is confusing and should be omitted.

Reply

This sentence has been deleted

Comment 4.

There is no description on how or whether at all the diagnosis was validated. The population-based registry mentioned before showed that approx. half of the cases reported as SJS/TEN proved to be no cases after standardized review blinded for exposures. Do the authors really believe that the rate of false diagnoses is lower in their compilation of spontaneous reports?

I strongly doubt this.

Reply

We have stated this as a limitation of the study. It is not possible to validate the SJS/TEN reported to VigiBase.

Comment 5

Since in a number of years following the approval of LTG in Europe it was administered as an add-on drug, it is no surprise that many patients received treatment of LTG and valproic acid (VPA) in parallel. However, the case-control study the authors quote as ref. 4 could demonstrate that the risk is confined to LTG and not to VPA. If the authors want to show a risk for VPA, they should look at the SJS/TEN-cases attributed to VPA w/o LTG-use and investigate the time latency between beginning of drug use and onset of the adverse reaction. If their cases are truly SJS/TEN and not erythema multiforme (EM), they will find a completely different pattern. Therefore, the conclusion that the risk to develop SJS/TEN is higher when LTG and VPA are used concomitantly than LTG alone is wrong.

Pharmacologic investigations, however, have shown that the half-life of LTG is longer when taken together with VPA. Therefore, it was advised that VPA should be stopped as well when a patient developed SJS/TEN after the use of LTG, but can be re-administered when the skin has healed. But this is a different topic.

Reply:

The research design (with ref A) already concedes the fact that LTG is the aetiological agent for all the cases and comparator. Our research aim was to identify additional risk factors associated with SJS/TEN in children who received LTG. We did not aim to show ‘a risk for VPA’ and investigating the time latency between the beginning of drug use and onset of the adverse reaction will not answer our research question. The effect of LTG+VPA was identified from exploratory analyses/screening of a range of variables/drugs (some reported in table 1 as top 5) and not from a study designed to specifically elicit an association between VPA+LTG and SJS/TEN.

Reference 4 cited in the manuscript did not explore the effect of VPA co-medication with LTG on the risk of SJS/TEN. It is unlikely that the high frequency of adjunctive LTG and VPA use in the immediate post marketing authorisation period in Europe will affect our outcome, since both cases and comparator (ref A) are subjected to the same bias. We did not conclude in this manuscript that ‘the risk to develop SJS/TEN is higher when LTG and VPA are used concomitantly than LTG alone’

Comment 6.

According to treatment guidelines, It is obvious that carbamazepine and phenobarbital are less likely to be combined with VPA than LTG. Therefore, this analysis as well as table 2 is misleading and should be omitted.

Reply

The selection of these drug combinations was solely for the purpose of comparison, since both CBZ and PBT are common causes of SJS/TEN. We have however deleted these as suggested.

Comment 7

The fact that SJS/TEN occurred within 8 weeks after beginning of drug use was shown in two different European studies, as references 4 and 5 show (not only in one, as stated in the manuscript; ref.5). Thus, statement a) under the headline “What this study adds” is not correct.

Reply

We did not claim that this finding is new. As a precursor to statement ‘a’ in ‘what the study adds’ we stated that the results of this study strengthen previous findings.

Comment 8

The second statement under this heading is incorrect as well or at least there is no proof at all that the statement “VPA and LTG comedication increases the risk of SJS/TEN” is true.

Reply

We have amended the b part of ‘what the study adds’

Comment 9

The limitations of the study have been described, but in addition, it should be stated that not only cases of EM may have been misdiagnosed as SJS/TEN, but also cases of other cutaneous conditions including maculopapular exanthems etc

Reply

The sentence has been modified