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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Risk of toxic epidermal necrolysis and Stevens-Johnson syndrome associated with benzodiazepines: a population-based cohort study

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Abstract
Purpose We aim to estimate the incidence of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) among tetrazepam users and compare it with benzodiazepine users in a Spanish primary care database (BIFAP). The incidence in the general population (GenPop) and among phenytoin new users (as a positive control) was also estimated.
Methods We identified a cohort of GenPop free of SJS/TEN (N=3,155,364). Cohort entry was the date after 1 year of register with the physician during 2001–2011. No age restrictions were applied. Patients were followed from entry up to the first of the following: a record of SJS/TEN (potential cases), death, end of information, or December 2011. History of potential cases were manually reviewed blinded to exposure and considered "probable" when diagnosed in referral reports. Three cohorts of patients newly prescribed with benzodiazepines (N=531,813), tetrazepam (N=343,568), or phenytoin (N=4993) were extracted from the GenPop cohort. Incidence rate (cases per million person-years (py)) for the GenPop and cumulative incidence (per million new users) during the first 9 weeks after each drug prescription were computed.
Results In the GenPop, 48 probable cases (38 SJS and 10 TEN) were identified (3.21/million py; 3.37 in men and 2.94 in women). In the benzodiazepines cohort, 2 probable TEN cases was identified (3.76/mill.). In the tetrazepam cohort, 1 probable SJS/TEN case was identified (2.91/mill.). In the phenytoin cohort, 4 probable cases (2 SJS and 2 TEN) were identified (801.12/mill.).
Conclusions The incidence of SJS/TEN in tetrazepam users was very rare and similar to benzodiazepines users. The incidence in the GenPop and among users of phenytoin agreed with the literature.

Keywords Stevens-Johnson syndrome · Toxic epidermal necrolysis · Tetrazepam · Benzodiazepines · Phenytoin · Incidence · Cohort study

Introduction/Aim

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are serious cutaneous disorders, which are drug-induced in the majority of cases (around three quarters of cases altogether) [1], although other factors may also play a role in some patients. More than 100 drugs have been described to be associated with these serious cutaneous adverse reactions (SCARs) [2–4], and few of them have been identified as strong risk factors, namely nevirapine, lamotrigine, carbamazepine, phenytoin, phenobarbital, cotrimoxazole, and other anti-infective sulfonamides, sulfasalazine, allopurinol, oxicam-NSAIDs, chlormezanone, and corticosteroids [3, 5]. SJS, TEN, and SJS/TEN overlap are severity variants of the same disease entity, sharing the same pathogenic and etiologic factors [4, 6, 7]. Although the incidence of SJS/TEN is low in the general population

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(1.1–7.1 SJS and 0.5–1.3 TEN per million patients and year [4, 8–13]), these reactions may severely disable previously healthy people or be fatal (20–25 % [14]).

SCARs are a frequent cause for regulatory actions, being the second most important cause of drug withdrawal after acute live injury [15]. Recently, tetrazepam-containing medicines have been suspended throughout the European Union due to the unfavorable benefit-risk balance [16], mainly due to its limited evidence on efficacy and the reported cases of serious skin reactions (including SJS, TEN, and drug reaction with eosinophilia and systemic symptoms (DRESS)). Tetrazepam is a benzodiazepine that was approved in Europe in the 1960s for the indication of painful muscle contractures and spasticity [17].

The aim of this study was to estimate the incidence of SJS/TEN among tetrazepam new users and compare to the one obtained in a cohort of benzodiazepines new users. As a positive control, we also estimated the incidence of SJS/TEN among phenytoin new users (a well-known drug-inducing SCARs). Incidence in the general population was firstly computed in order to obtain a background rate of SJS/TEN recorded in BIFAP.

Methods

Source of data

BIFAP (Base de Datos para la Investigación Farmacoepidemiológica en Atención Primaria) is a longitudinal population-based database of anonymized electronic medical records of primary care practitioners and pediatricians (PCP) from nine different regions in Spain [18]. BIFAP is fully funded by the Spanish Agency on Medicines and Medical Devices (AEMPS), belonging to the Department of Health, in collaboration with the participant regions. Spain has a public national health service (named SNS), where PCPs act as gatekeepers for and receiver of information from primary and secondary care. Almost all population is registered with a local PCP under the Spanish SNS. PCPs participate in BIFAP on a voluntary basis. The database includes anonymized information from patients assisted by 2324 physicians (84 % general practitioners and 15 % pediatricians). Data available include patient demographics, clinical events (coded through ICPC medical terms dictionary [19]), free text notes, specialist referrals, and laboratory test results of around 4 million patients (19 million patient-years) covering around 8.9 % of the Spanish population (19.1 % of the total population from participating regions). Prescriptions are automatically recorded in BIFAP once written.

Study design

We performed the study using the following cohorts: (1) general population, (2) benzodiazepine new users, (3) tetrazepam new users, and (4) phenytoin new users.

Study population

Firstly, we identified retrospectively a cohort of general population free of previous SJS and TEN records at entry date. Cohort entry was the date after 1-year enrollment with the PCP during the study period (2001–2011). No age restrictions were applied (Fig. 1). The cohort was formed by 3,155,364 patients and was followed from cohort entry date to the first of the following events (stop date): a diagnosis record of SJS or TEN, death, end of available information, or end of study period (31 December 2011).

Three cohorts of patients newly prescribed with benzodiazepines (N=531,815; Anatomical Therapeutic Chemical code (ATC): N03AE, N05BA, N05CD), tetrazepam (N=343,568; ATC07: M03BX07), or phenytoin (N=4993; ATC: N03AB02, N03AB05, N03AB52) during study period were extracted from the general population cohort. A patient was considered a new user of the drug of interest when he received a first prescription ever between cohort entry and stop date. All the three cohorts were followed up from first prescription to the occurrence of one of the following events: a diagnosis record of SJS or TEN, death, end of available information, or end of study period, whichever came first (Fig. 1). Patients prescribed with tetrazepam were excluded from the benzodiazepine cohort.

Case definition and ascertainment

Cases were patients with a recorded diagnosis of SJS or TEN during follow-up. There is no ICPC code for SJS/TEN. To detect all potential cases of SJS and TEN, a broad computer search of string texts identifying the disease of interest (i.e., "necrolisis epidermica", "Lyell", or "Stevens-Johnson") was performed in the patients' medical records. Through this computer search, 174 potential cases were identified. The clinical profile of these potential cases were manually reviewed independently and blinded to drug exposure by two authors (EM and FdA) and classified as probable, possible, or non-case. A case was classified as "probable" when the diagnosis of SJS/TEN was confirmed in the hospital discharge report after admission or in a specialist letter (dermatologist, allergologist); "possible" when the medical profile included a diagnosis of SJS/TEN in the absence of additional information from hospital or specialist confirming the diagnosis; and as "non-case" when referring to past episodes, confirming other skin reactions or consultations of patient fear to suffer SCAR. In general, the clinical description of the episode in the patient

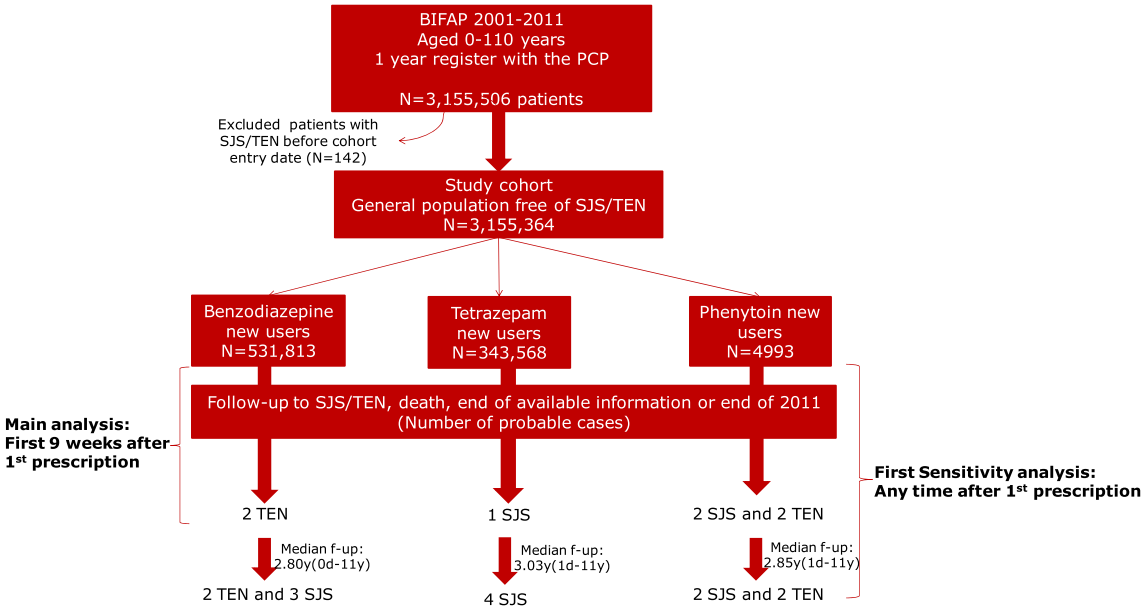


Fig. 1 Study cohorts and SJS or TEN cases ascertainment and cumulative incidences among drug-specific cohorts

profile was not considered enough nor required to classify cases, but it was used to support (when strongly compatible) or rule out (when not compatible) the diagnosis recorded.

For cases included in benzodiazepines, tetrazepam, and phenytoin cohorts, we applied the ALDEN algorithm for causality assessment [20].

Statistical analysis

For the general population cohort, we estimated the incidence rate of SJS/TEN using probable cases in the numerator and person-years of follow-up in the denominator. Cumulative incidence was also calculated by dividing the number of cases by the total number of patients entering the cohort.

For drug-specific cohorts, main analysis included only probable cases and cumulative incidences were computed by dividing probable SJS/TEN cases occurring in the first 9 weeks after first prescription by the total number of new users (patient at risk) [1]. Two additional sensitivity analyses were performed: (1) by extending the risk time window including probable cases detected any time after the first prescription and (2) by widening the case definition including both probable and possible cases in the first 9 weeks.

Due to the immuno-allergic mechanism of SCAR, where hazard is not constant over time, but rather occurs at the beginning of treatment, the proper metric to compute absolute risk is cases occurring in a short time over the number of patient at risk [21]. We used a risk time window of 9-weeks because 90 % of SJS/TEN appear in 9 weeks after exposure [1].

Age- and sex-adjusted risk ratio of SJS/TEN associated to tetrazepam versus other benzodiazepines was estimated by Mantel-Haenszel pure count data [22].

Results

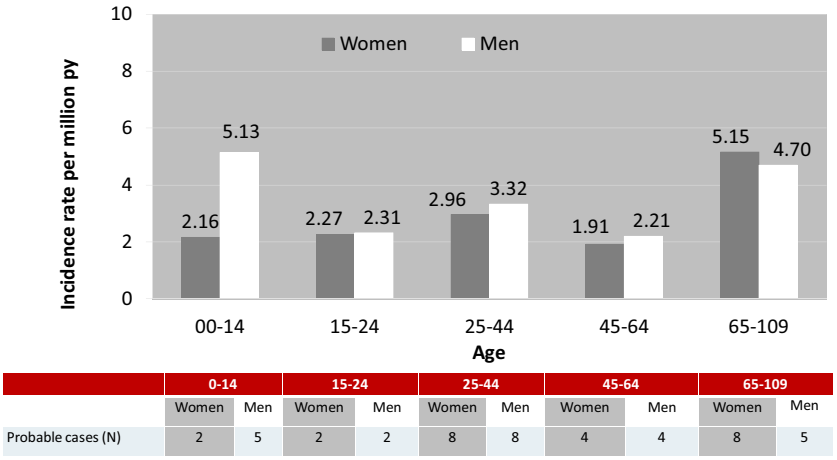
Incidence of SJS/TEN in the general population

In the general population cohort (N=3,155,364; during more than 15 million person-years of follow-up: median of 4.58 years), 48 probable cases (33 with a hospital discharge letter at least and 15 with a specialist letter) and 44 possible cases were identified. Out of the 48 probable cases, 38 were recorded as SJS and 10 were recorded as TEN, 24 were women (mean age 46.61, SD ±23.06, age range 3–85) and 24 men (mean age 39.05, SD ±23.81, age range 2–79). Out of the 44 possible cases, 36 were recorded as SJS, 4 as TEN, and 4 as SJS/TEN.

The incidence rate of SJS/TEN in the general population cohort was 3.14 probable cases per million person-years of follow-up (3.37 in men and 2.94 in women). Figure 2 shows the distribution of the incidence rate by age and sex. Highest incidence was found among patients aged ≥65 years and boys aged 0–14 years. In terms of cumulative incidence, the resulting figure was 15.21 probable cases per million patients (16.31 for men and 14.28 for women) in a maximum follow-up of 11 years (Table 1).

Incidence of SJS/TEN among benzodiazepine new users

We identified a total of 531,813 new users of benzodiazepines (excluding tetrazepam) who were followed up a median of



	0-14		15-24		25-44		45-64		65-109	
	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men
Probable cases (N)	2	5	2	2	8	8	4	4	8	5

Fig. 2 Incidence rate of SJS or TEN cases in general population by age and sex in BIFAP during the study period 2001–2011

2.80 years. Out of them, 5 probable cases (3 recorded as SJS and 2 as TEN) and 6 possible cases (4 recorded as SJS and 2 as SJS/TEN) were identified over the follow-up. Only 2 probable TEN cases occurred within the first 9 weeks after a benzodiazepine first prescription, both exposed to lorazepam.

The first case was a woman aged 27 years prescribed with lorazepam 7 days before the recorded TEN; according to the PCP free comments, this case was triggered by carbamazepine or amoxicillin-clavulanic acid. Lorazepam continued to be prescribed after the episode with no recurrence registered (ALDEN score: very unlikely). The second case was a man aged 69 years prescribed with lorazepam 2 months before the recorded TEN episode, but according to the PCP free text comments, TEN was attributed to metronidazol. This patient was under immunosuppressant therapy after renal transplant, which was finally rejected, and died (the cause of death was not recorded) (ALDEN score: unlikely).

The remaining 3 probable SJS cases occurred more than 1 year after the first benzodiazepine prescription (ALDEN score: unlikely or very unlikely). The 6 possible cases occurred more than 1 year after the first prescription of a benzodiazepine (ALDEN score: unlikely or very unlikely).

Thus, the corresponding cumulative incidence in the first 9 weeks among patients exposed to benzodiazepines was 3.76 probable cases per million new users. In the first sensitivity analysis, the cumulative incidence any time after the first benzodiazepine prescription was 9.40 (95 % CI 3.05–21.90) probable cases per million new users (in a maximum of 11 years). In the second sensitivity analysis, no "possible" cases were found during the time to onset of 9 weeks after benzodiazepines first exposure, so incidences did not change versus main analysis (Table 1).

Incidence of SJS/TEN among tetrazepam new users

We identified a total of 343,568 new tetrazepam users who were followed up a median of 3.03 years. Out of them, 4 probable SJS and 6 possible SJS cases were identified any time after the first exposure. Only 1 probable case occurred within the first 9 weeks of treatment (exactly 38 days after tetrazepam first prescription). That case was a woman aged 69 years diagnosed with lung adenocarcinoma and under radiotherapy together with many other drugs. According to the PCP notes, the episode was attributed to phenytoin, which has been newly prescribed 18 days before SJS diagnosis (ALDEN score for tetrazepam: unlikely). The remaining 3 probable cases occurred more than 1 year after the first tetrazepam prescription (ALDEN score: unlikely or very unlikely) and all possible cases occurred more than 3 months after (ALDEN score: unlikely or very unlikely).

Thus, the corresponding cumulative incidence in the first 9 weeks among those exposed to tetrazepam was 2.91 per million new users. In the first sensitivity analysis, the cumulative incidence any time after the first tetrazepam prescription was 11.64 probable cases per million new users (in a maximum of 11 years). In the second sensitivity analysis, no "possible" cases were found during the time to onset of 9 weeks after tetrazepam first exposure, so incidences did not change versus main analysis (Table 1).

Age- and sex-adjusted risk ratio of SJS/TEN associated to tetrazepam versus other benzodiazepines was 1.42 (95 % CI 0.39–5.17).

Incidence of SJS/TEN among phenytoin new users

We identified a total of 4993 new users of phenytoin who were followed up a median of 2.85 years. Out of them, 4 probable cases (2 SJS and 2 TEN) and no possible SJS/TEN cases were identified any time after phenytoin first exposure. The 4 probable SJS/TEN cases (a man aged 52 years and three women aged 40, 47, and 69 years) were recorded within 9 weeks since phenytoin first prescription. No other culprit drugs were declared in patient's clinical history (ALDEN scores: probable).

Table 1 Number of SJS or TEN cases and incidence in BIFAP general population during 2001–2011

	General population	Cohorts of exposed patients[b]		
		Other benzodiazepines cohort	Tetrazepam cohort	Phenytoin cohort
Number of patients in the cohort	3,155,364	531,813	343,568	4993
Women	53.37 %	63.65 %	62.61 %	45.66 %
Mean age (SD)	37.41 (22.32)	49.58 (19.20)	44.70 (16.09)	60.13 (19.30)
Median of follow-up (years) (range)	4.58 (1 day to 11.00 years)	2.80 (0 day to 10.99 years)	3.03 (1 day to 10.99 years)	2.85 (1 day to 10.99 years)
Follow up to anytime after cohort entry				
Probable cases anytime after cohort entry	38 SJS and 10 TEN	3 SJS and 2 TEN	4 SJS	2 SJS and 2 TEN
Incidence rate per 10^6 patients-years (95 % CI)	3.14 (2.32–4.17)	NA	NA	NA
Cumulative incidence per 10^6 patients (95 % CI)	15.21 (11.20–20.20)	9.40 (3.05–21.90)	11.64 (3.17–29.80)	801.12 (218.30–2049.90)
Follow up to 9 weeks after first prescription				
Probable cases during 9 weeks after the first prescription	NA	2 TEN	1 SJS	2 SJS and 2 TEN
Cumulative incidence per 10^6 patients (95 % CI)	NA	3.76 (0.46–13.60)	2.91 (0.07–16.20)	801.12 (218.30–2049.90)
Follow up to 9 weeks after first prescription				
Probable and possible[a] cases during 9 weeks after the first prescription	NA	2 TEN	1 SJS	2 SJS and 2 TEN
Cumulative incidence per 10^6 new users	NA	3.76 (0.46–13.60)	2.91 (0.07–16.20)	801.12 (218.30–2049.9)

[a] No possible case was identified in the first 9 weeks in any cohort

[b] Benzodiazepine and tetrazepam cohorts were mutually exclusive

NA not applied due to the nature of the design. *IR* incidence rate, *py* person-years, *TEN* toxic epidermal necrolysis, *SJS* Stevens-Johnson syndrome

Thus, the corresponding incidence in the first 9 weeks after the first phenytoin prescription was 801.12 probable cases per million new users. In the first and second sensitivity analysis, no extra cases were found, so incidences did not change versus main analysis (Table 1).

Discussion

In this cohort study, performed in a Spanish primary care population between 2001 and 2011, the risk of SJS/TEN within 9 weeks after tetrazepam first exposure, was very rare (less than 1/100,000 new users) and similar to that observed with other benzodiazepines. We also detected a high incidence of SJS/TEN associated with phenytoin (around 1 in 1000 new users) compatible with the one reported in the literature [2], which suggests that BIFAP database is sensitive to detect drug-induced SJS/TEN cases. This sensitivity is also suggested by the incidence observed in BIFAP general population, which falls within the incidence range found in the literature [4, 8–13].

The incidence of SJS/TEN among benzodiazepines and tetrazepam users is of interest, because recently, tetrazepam-containing medicines were suspended throughout the European Union due to an unfavorable benefit-risk balance [16]. The evidence of clinical efficacy was found limited in the authorized indications (i.e., painful contractures and spasticity) [23–25], and its safety was compromised by the reporting of rare but serious cutaneous adverse reactions, including SJS/TEN, among others. This safety evaluation was mainly based on cases reported to the French National Pharmacovigilance over the period 1969–2012, including 33 SJS (1 fatal) and 33 TEN (9 fatal) cases associated with tetrazepam [16, 26]. According to a recent published review [27], 2 SJS and 4 TEN cases (1 fatal) were reported to the Spanish Pharmacovigilance Database (FEDRA) during the tetrazepam marketing period (1978–2013) and 6 SJS and 4 TEN reported to the Food and Drugs Administration of U.S. from 2004 to 2012 [28]. Cases of SJS [29–31] and TEN [32–34] associated with tetrazepam have been also described in the literature.

SJS or TEN associated with other benzodiazepines have been scarcely reported in the literature, i.e., 2 TEN episodes under treatment with flurazepam [35] and clobazam [36], respectively, and 3 SJS episodes, i.e., 1 after chlordiazepoxide overdose [37] and 2 under treatment with clobazam [38] and nitrazepam [39], respectively, both in combination with anticonvulsant drugs.

In spite of these communications of cases to pharmacovigilance registers and publications, and the high use of benzodiazepines in Western countries [40], a formal study estimating the risk of SJS/TEN associated with these drugs is lacking in the literature. Few data sources are available to evaluate SCARs in a population base. RegiSCAR [41] is an international registry of SCAR cases, which was used to assess the risk of tetrazepam to induce SCARs. In this study, the researchers concluded that data available did not suggest a high risk [42].

In an attempt to double estimate the tetrazepam-specific SJS/TEN incidence, we consulted the Spanish register "PIELenRed" [43] that collects all cases of SJS/TEN detected in a network of major hospitals in Madrid (including the two reference hospitals having Great Burn Units where all TEN cases occurring in the region are assisted). According to PIELenRed, 10 cases of SJS/TEN were attended from 2011 to 2013 in those hospitals, and no one was reported exposed to tetrazepam. Taking into account that around 190,000 new users of tetrazepam were estimated in Madrid for that period (according to BIFAP prescriptions), the maximum tetrazepam-specific SJS/TEN incidence compatible with zero cases would be 15.9 in 1 million exposed patients (i.e., 95 % CI upper limit, after application of the "rule of threes" [44]), but the true incidence may be much lower.

RegiSCAR and PIELenRed evaluations are consistent with the very low risk of SJS/TEN associated to tetrazepam estimated in the present study. Moreover, all SJS/TEN episodes among tetrazepam or benzodiazepines new users recorded in BIFAP were reported to be triggered by other drugs, i.e., by carbamazepine or amoxicillin-clavulanic acid and metronidazol in the 2 cases exposed to benzodiazepines and by phenytoin in the case exposed to tetrazepam. However, although no mention of the implication of tetrazepam, other benzodiazepines or interaction among drugs was declared in the patients' clinical profiles, such implication cannot be discarded with our data, nor a cross-sensitivity with anticonvulsant drugs.

In order to show the sensitivity of BIFAP database to detect SJS/TEN episodes, we studied its incidence, both in the general population and in phenytoin users, a drug well known to induce SJS/TEN. The estimated incidences fall within the range found in the literature, i.e., 1 to 7 SCAR cases per million population per year in the general population [4, 8–13] and 6.9 to 8.3 per 10,000 new users for phenytoin [2]. However, we found an unexpected high incidence of SJS/TEN among boys in the general population. It could be that part of these cases was actually erythema exsudativum multiforme majus (EEMM) wrongly diagnosed as SJS/NET. As shown previously in studies based on registries, some SJS/TEN cases were actually other conditions such as generalized bullous-fixed drug eruption or EEMM [1, 5–7]. The complexity of diagnosis and its consequent misclassification is also reflected in the literature as the broad range of incidences for general population above referred. A relevant rate of misdiagnoses in our study would have led us to overestimate the incidence of SJS/TEN.

The main strength of the current study is the numerous benzodiazepine and tetrazepam users that empowered the analysis to find exposed cases if the incidence were 1 in 100,000 or greater. Other strength is related to the fact that PCPs are the gatekeepers of the Spanish National Health System, and so patients, even those discharged from hospitals, receive continuous checking and treatment by their PCP. Therefore, non-fatal hospitalized SCARs are expected to be completely recorded in BIFAP. Moreover, benzodiazepines are only available under prescription, so it would be very unlikely to have exposed cases with no prescription recorded.

Some limitations deserve mention. Firstly, adherence to treatment cannot be confirmed. Secondly, case ascertainment was based on hospital or specialist diagnoses entered by PCP in clinical records. No hospital discharge or specialist reports were retrieved, nor histopathology results or photographs were available. Therefore, we did not have the possibility of submitting the cases for a thorough review. In addition, as aforementioned, the misclassification of EEMM as SJS/TEN could be present in our study, particularly among youngest boys.

On the other hand, the exclusion of what we called possible cases may have led us to underestimate the incidence. This is the reason why we report the incidence including both probable and possible cases in a sensitivity analysis. Thirdly, although patients normally get their prescriptions from the PCP, including those prescribed by specialists, we could have missed phenytoin new users receiving a first prescription in specialist setting and developing a SJS/TEN before visiting their PCP. If this had occurred, we would have underestimated the incidence associated with phenytoin. Finally, fatal SJS/TEN cases may not be fully recorded in BIFAP; this would lead us to underestimate the incidence around one fourth assuming a case fatality rate of SJS/TEN of 20–25 % [14].

We stress the need for exhaustive registries of SCAR to describe SCAR episodes and suspected drugs, the use of electronic medical records as a tool to estimate drug-specific SJS/TEN incidences in the general population, as well as the multiple setting professional networking [27], in order to identify risk factors and better approaches to improve the prognosis of these rare but important drug-induced diseases.

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Conflict of interest The authors declare that they have no conflict of interest. The views expressed here do not necessarily represent the views of the co-authors' respective companies or organizations.

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