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EDITORIAL

The Value of Sensitivity Analyses in Assessing the Risk of Two Rare Neurological Adverse Events and Pseudoephedrine Use

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1 Introduction

Determining the risk of rare adverse events (AEs) related to prescription medicines is challenging, and this challenge is further compounded when considering risks of nonprescription medicines. Nonprescription medicines are frequently used without direct clinical supervision, and active surveillance systems for potential adverse drug events are generally focused on pre-specified outcomes and prescription medicines. Additionally, when AEs are assessed using passive surveillance systems, such systems often lack measurement of drug exposure, unexposed controls for comparison, and comprehensive information to control for factors that could confound causality and influence the frequency and severity of AEs.

A foundational method used in risk assessment is comparing the observed rate of an AE to the population background incidence rate to contextualize the potential causality between the exposure and outcome and better understand the magnitude of harm [1]. Historically, information regarding the baseline rate of AEs is often limited, as it may be derived from case series or studies that contain very few events. However, population incidence for many conditions can be obtained from national or regional discharge databases [2, 3] and may be increasingly available from real-world data sources [4]. Nonetheless, even when background incidence rates are available, potential differences in patient populations, limited drug exposure data, and under-reporting of AEs are important challenges to consider, particularly for nonprescription medicines. To address these challenges, sensitivity analyses, wherein key parameters are identified and varied, can be used to enhance observed to expected risk assessments. We used this approach to examine the relationship between pseudoephedrine exposure and two rare neurological conditions.

2 Sensitivity Analyses to Augment Assessment of Rare Events Potentially Associated with Pseudoephedrine Use

In 2023, the National Agency for the Safety of Medicines and Health Products (ANSM) of France raised concerns about the safety of pseudoephedrine, an active ingredient in many nonprescription nasal decongestants, and initiated an Article 31 referral under Directive 2001/83/EC to the European Medicines Agency (EMA) for pharmacovigilance review. The referral was based on case reports of posterior reversible encephalopathy syndrome (PRES) and reversible cerebral vasoconstriction syndrome (RCVS) in individuals using pseudoephedrine-containing medicines. Following this, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) conducted a comprehensive analysis of available data, including AE reports to EudraVigilance and worldwide scientific literature, to evaluate the risk of PRES and RCVS associated with pseudoephedrine. Between 2007 and 2023, 34 cases of PRES or RCVS were reported (18 cases from the European Economic Area [EEA]), which were assessed to be possibly or probably linked to pseudoephedrine. Most cases were resolved; 5 cases were

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associated with sequelae, and no cases were fatal [5]. Apart from the compilation and extensive review of this case series by PRAC, there were no additional epidemiologic data available that directly assessed the relationship between pseudoephedrine and these rare neurological events.

We sought to combine the PRAC-reviewed case series data with estimates of pseudoephedrine exposure to calculate an average annual reporting rate of PRES and RCVS potentially associated with pseudoephedrine use. This rate was defined as the total number of PRES and RCVS cases identified in the PRAC review divided by the estimated average number of individuals exposed to pseudoephedrine per year. We conducted a series of sensitivity analyses, varying key parameters, in order to compare a range of plausible annual reporting rates with the expected population background rate, derived from published epidemiologic studies of PRES and RCVS. To evaluate the effect of uncertainties on the annual reporting rate, we varied: (1) the estimated pseudoephedrine exposure; (2) the geographic scope; (3) the potential underreporting rate; and (4) the number of cases, focusing on subgroups of interest (Table 1).

The base-case scenario included all 18 cases from EEA countries identified between 2007 and 2023. The population prevalence of pseudoephedrine exposure was estimated to be 1.5% of the average annual EEA population during this period. This estimate applied the mid-point estimate of a study on nasal decongestants in France by Grimaldi-Bensouda et al., which estimated weekly pseudoephedrine use to be 1–2% of the population [6].

Due to differences in product availability across EEA countries, utilization patterns from Grimaldi-Bensouda et al. may not be generalizable to countries other than France. To account for country-specific variation in the use of pseudoephedrine-containing products, we modelled an alternative scenario using sales data from IQVIA Global OTC Insights, estimating exposure based on the number of packages of pseudoephedrine-containing products sold in 16 EEA countries between 2011 and 2022. We conservatively assumed that, on average, individuals experience four colds per year and purchased and completely used one packet of a pseudoephedrine-containing product per episode to calculate a sales-based estimate of the exposed population. This scenario included France and 15 other countries with pseudoephedrine sales data available, thereby minimizing the plausibly exposed population and maximizing the plausible estimated reporting rate calculated from sales data.

We also explored the impact of varying the geographic scope on reporting rates, given that EEA countries may vary with respect to the comprehensiveness of their national post-marketing surveillance systems as well as clinician awareness of PRES and RCVS. Of the 18 cases identified in EEA countries, 16 cases were reported from France. The French Pharmacovigilance system is a coordinated network of 31 centers, to which clinicians are required to report serious adverse reactions [7]. In addition, for over a decade, there has been education and specific efforts to identify neurovascular complications of vasoconstrictors in France [8]. Therefore, a scenario applying data solely from France was created to estimate the frequency of PRES and RCVS in which under-reporting would be minimized.

In general, adverse drug events are underreported to passive post-marketing surveillance systems. In a systematic review of underreporting, Hazell and colleagues estimated that the underreporting of AEs overall was approximately 95%, decreasing to 80% for serious and severe AEs [9, 10]. Although PRES and RCVS are considered severe AEs, often diagnosed and treated in hospital, we conservatively adjusted all scenarios to assume 95% underreporting.

After applying a series of plausible scenario parameters, the estimated annual reporting rates of PRES and RCVS after pseudoephedrine exposure ranged from 0.004 per 100,000 to a maximum adjusted annual reporting rate of 2.1 per 100,000 individuals (Fig. 1). Applying a 1.5% exposure estimate from Grimaldi-Bensouda et al. resulted in a higher reporting rate than any scenario using sales data. We then identified available data on the background population incidence of PRES and RCVS. A claims analysis of data from non-federal US hospitals reported 2096 cases of PRES among 7,581,668 hospitalizations over a 3-year period [11]. We extrapolated the expected annual incidence of PRES hospitalizations to be 2.3 per 100,000 adults in the USA. Two studies reported annual incidences of 0.30 and 0.45 RCVS hospitalizations per 100,000 adults per year in the USA using the same hospital system [12, 13].

Thus, even after adjusting for 95% underreporting, the estimated adjusted reporting rate of PRES and RCVS after pseudoephedrine use did not exceed the expected background population incidence of PRES and RCVS in any scenario. The sensitivity analysis scenario limited to France and adjusted for 95% underreporting resulted in the highest reporting rate (2.1 per 100,000 adults). The 16 cases reported from France exceeded the number reported in any other country. Elevated awareness and surveillance may have led to disproportionately high case counts, particularly of RCVS cases identified in France. In the past decade, there have been several studies conducted in France regarding RCVS [14–17] and the ongoing development of an international RCVS registry [18].

Table 1 Parameter adjustments for estimating plausible annual reporting rates of PRES and RCVS after pseudoephedrine use in the EEA

Parameter	Scenario	Scenario description	Value
Population at risk	Base case	1.5% of annual population in EEA countries	6.7 million people
	Parameter adjustments	1.5% of annual population in major EEA markets (i.e., France, Germany, Italy, and Spain)	3.8 million people
		1.5% of annual population of France only	1.0 million people
		Total number of packs of pseudoephedrine-containing products sold in 16 EEA countries between 2011–2022, assuming 4 packs per individual annually[a]	15.5 million people
Geographic scope	Base case	All EEA countries	18 PRES and RCVS cases
	Parameter adjustment	Only cases in France	16 PRES and RCVS cases
		Only cases from major EEA markets (i.e., France, Germany, Italy, and Spain)	16 PRES and RCVS cases
Adjustment for underreporting	Base case	No adjustment to account for underreporting	No adjustment to number of cases
	Parameter adjustment	95% underreporting	20 × number of cases
Subgroups of interest	Base case	All PRES/RCVS identified by the EMA in EEA countries between 2007–2023	18 PRES and RCVS cases
	Parameter adjustment	PRES cases only identified by the EMA in EEA countries between 2007–2023	4 PRES cases
		RCVS cases only identified by the EMA in EEA countries between 2007–2023	14 RCVS cases
		All PRES/RCVS with sequelae identified by the EMA in EEA countries between 2007–2023	6 PRES and RCVS cases

EEA European Economic Area, *EMA* European Medicines Agency, *PRES* posterior reversible encephalopathy syndrome, *RCVS* reversible cerebral vasoconstriction syndrome

[a]Sixteen countries with pseudoephedrine sales data available from IQVIA Global OTC Insights: Austria, Belgium, Bulgaria, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Poland, Portugal, Spain, and Sweden

3 Regulatory Review of Pseudoephedrine and Actions Relating to PRES and RCVS

The methodology of this sensitivity analysis and our findings that the estimated reporting rate of PRES or RCVS attributable to pseudoephedrine use did not exceed the reported background incidence in the general population, even after plausible adjustments, were submitted to the EMA. Following the review of all submitted safety and efficacy data and consultation with an ad hoc expert group, in January 2024, the EMA concluded that the benefit-risk profile of pseudoephedrine-containing products is acceptable for continued availability as nonprescription medicines, with updates to the Patient Information Leaflet, Summary of Product Characteristics, and a direct healthcare professional communication [19]. These materials educate healthcare professionals and patients that PRES and RCVS have been reported as a very rare side effect with the use of pseudoephedrine-containing medicines and provide additional guidance on appropriate use.

4 Future Use of Sensitivity Analyses to Enhance Limited Data on Potential Adverse Events

Assessing the potential association of an AE and medication use often involves making decisions with limited data. Data are typically even more limited for nonprescription medicines, as medically unsupervised use complicates the collection and reporting of patient and drug exposure information. By leveraging multiple sources to provide estimates for uncertain parameters, sensitivity analyses can provide a structured way to patently consider plausible scenarios and enhance the utility of available pharmacovigilance data. Data on drug exposure and population incidence data may not be available in every instance; however, the sensitivity analysis described in this report provides one example of using such data to extend the utility of AE case reports. While PRES and RCVS have been reported subsequent to pseudoephedrine use, finding that the estimated rates do not exceed published population incidence adds context to the potential magnitude of risk associated with pseudoephedrine use.

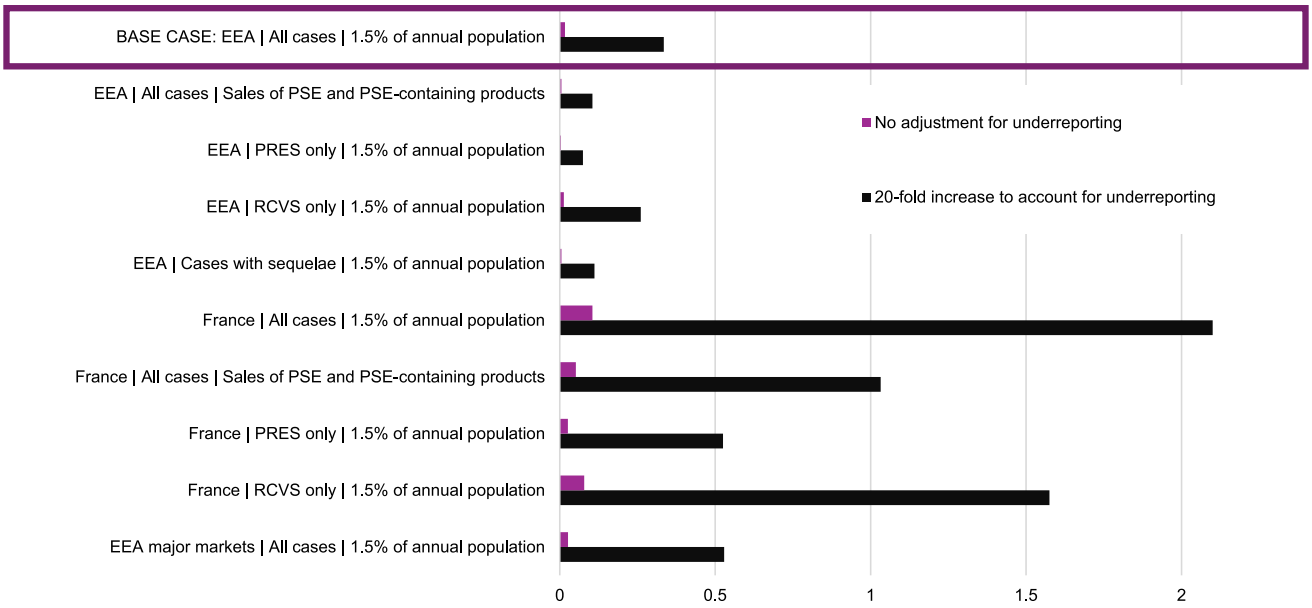

Fig. 1 Estimated base case and adjusted annual reporting rates of PRES and RCVS per 100,000 after pseudoephedrine use in the EEA. *EEA* European Economic Area, *PRES* posterior reversible encephalopathy syndrome, *PSE* pseudoephedrine, *RCVS* reversible cerebral vasoconstriction syndrome

Declarations

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Conflict of interest Dr. Alexander is a past Chair of FDA's Peripheral and Central Nervous System Advisory Committee and co-founding Principal and equity holder in Stage Analytics. Dr. Alexander is an Editorial Board member of Drug Safety. Dr. Alexander was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. Ms. Chingcuanco is an employee of Stage Analytics. These arrangements have been reviewed and approved by Johns Hopkins University in accordance with its conflict of interest policies. Dr. Budnitz and Dr. Garg are employees of Kenvue, LLC.

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Availability of data and materials (data transparency) Not applicable.

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