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Pseudoephedrine: A Review and Benefit-Risk Assessment with Reference to the Risk of Posterior Reversible Encephalopathy Syndrome (PRES) and Reversible Cerebral Vasoconstriction Syndrome (RCVS)

Ronald Eccles*

Cardiff School of Biosciences, Cardiff University, Cardiff, UK
Email: Ronald.eccles@gmail.com

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Abstract

Pseudoephedrine (PSE) is a widely used nasal decongestant. A review by the European Medicines Agency has reported that PSE may be associated with risks of posterior reversible encephalopathy syndrome (PRES) and reversible cerebral vasoconstriction syndrome (RCVS). PRES and RCVS are rare but serious conditions that affect cerebral blood flow. This review discusses the pharmacology of PSE and potential risks for PRES and RCVS and concludes that considering the common use of PSE, with over 70 million packs of PSE taken each year in the European Union and the United Kingdom, and the rare occurrence of PRES and RCVS, that the risks of developing PRES/RCVS on exposure to PSE are likely to be very low.

Keywords

Posterior Reversible Encephalopathy Syndrome (PRES), Reversible Cerebral Vasoconstriction Syndrome (RCVS), Pseudoephedrine, European Medicines Agency

1. Introduction

Pseudoephedrine (PSE) is widely used as an oral decongestant treatment for nasal and sinus congestion, and over 400 products containing PSE alone or in combination with other medicines, such as analgesics, antihistamines and cough medicines are marketed in the European Union (EU) and the United Kingdom (UK)

*Former Director of Common Cold Centre and Healthcare Clinical Trials (1988-2017).

[1]. A review by the European Medicines Agency (EMA) has found that PSE-containing medicines are associated with risks of posterior reversible encephalopathy syndrome (PRES) and reversible cerebral vasoconstriction syndrome (RCVS). PRES and RCVS are rare but serious conditions that affect the blood supply to the brain [2]. On 25 January 2024, EMA's human medicines committee (CHMP) endorsed the measures recommended by the Pharmacovigilance Risk Assessment Committee (PRAC) to minimise the risks of (PRES) and (RCVS) for medicines containing PSE. PRAC recommended that there was a need to inform healthcare professionals (HCPs) as early as possible by Direct Healthcare Professional Communication (DHPC) and update the product information for PSE concerning potential risks for PRES and RCVS. No fatal cases of PRES or RCVS have been reported, and most of the cases resolved following discontinuation of the medicine and appropriate treatment [2]. In response to EMA recommendation, the European Commission issued a Decision on 27 March 2024 that Marketing Authorisation Holders should amend their respective centralised and national marketing authorisations for products containing PSE to include reference to contraindications and special warnings concerning PRES and RCVS [1]. The pack instructions to patients now state that PSE should not be used in patients with severe or uncontrolled hypertension and severe acute or chronic kidney disease or failure. However, a post-authorization safety study was conducted in 151 cardiology centres and 78 neurology centres in France to assess the risk of MI and stroke after the use of vasoconstrictors (oral PSE or nasal drugs with vasoconstricting agents) found no increase in these adverse cardiovascular outcomes [3]. Additionally, it is recommended that HCPs should counsel patients to discontinue the use of PSE promptly and seek medical assistance if they experience symptoms suggesting PRES or RCVS, such as sudden onset of severe headache, confusion, vomiting, visual disturbances or seizures [4].

Considering the recent reviews by European regulatory authorities on the benefit-risk profile of PSE, it was considered useful to review the pharmacology of PSE relevant to any potential risk for the onset of PRES or RCVS.

2. Literature Survey

The starting point for the literature was the references in the PRAC Rapporteur's and Co-rapporteur's updated assessment reports on the benefit-risk assessment of PSE in relation to PRES and RCVS [5] [6]. Citation reports for relevant articles in the PRAC report were made on the Web of Science.

3. Structure of This Review

This review will be divided into the following sections: Indications for treatment with PSE, Pharmacology of PSE, Role of sympathetic nervous system in nasal and cerebral circulations, Efficacy of PSE as a decongestant, Benefits of treatment with PSE, Posterior Reversible Encephalopathy Syndrome (PRES), Reversible Cerebral Vasoconstriction Syndrome RCVS, Benefit-Risk Assessment of PSE, Conclusions, References.

4. Indications for Treatment with Pseudoephedrine

PSE is taken orally for the symptomatic treatment of congestion in the nasal cavity, paranasal sinuses and the Eustachian tube associated with acute upper respiratory tract viral infections (URTI) and allergic rhinitis [7]. Other indications include vasomotor rhinitis, and otitis media [8]. The main indications for treatment with PSE are nasal congestion associated with the common cold and flu and allergic rhinitis.

5. Pharmacology of Pseudoephedrine

PSE is a stereoisomer of ephedrine and has a structure similar to noradrenaline [9] as illustrated in **Figure 1**.

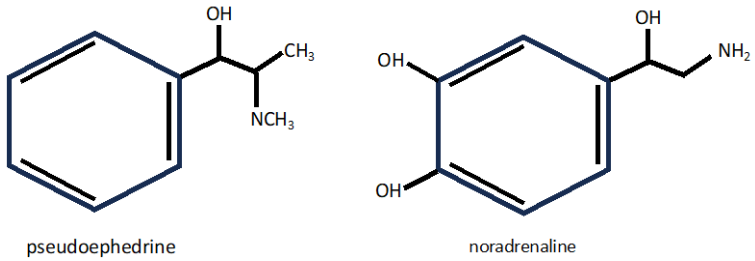

Figure 1. Structure of pseudoephedrine and noradrenaline.

PSE is a sympathomimetic with a mixed mechanism of action with both direct and indirect effects on alpha and beta adrenergic receptors [8] as illustrated in **Figure 2**. PSE exerts its indirect effects by inhibiting the uptake of noradrenaline [10] [11] and by displacing noradrenaline from sympathetic nerve endings [11].

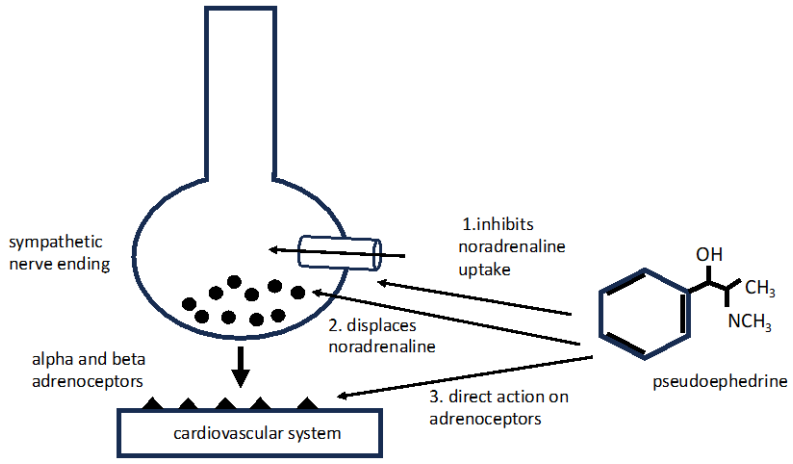

Figure 2. Mechanism of action of PSE in causing vasoconstriction. 1. Inhibits noradrenaline uptake into nerve endings and therefore increases concentration of noradrenaline around blood vessel and prolongs action of noradrenaline. 2. After entering nerve ending displaces noradrenaline which is released to act on adrenoceptors in blood vessels. 3. Acts directly on alpha and beta adrenoceptors on blood vessels.

PSE can also directly stimulate alpha and beta adrenoceptors on blood vessels

and cardiac beta receptors [11]. The cardiovascular effects of PSE are believed to be almost completely due to its actions on sympathetic nerve endings, causing noradrenaline release from the nerve endings and inhibiting uptake of noradrenaline into nerve endings, and PSE has little direct action on adrenoceptors. PSE acts on blood vessels via the release of noradrenaline, which acts on alpha 1 receptors to cause vasoconstriction. Noradrenaline also acts on beta receptors and causes an increase in heart rate by stimulation of beta 1 receptors.

Preclinical studies provide evidence that PSE acts via the release of noradrenaline from nerve endings. A study on anaesthetized rats reported that PSE caused a dose dependent increase in arterial blood pressure and heart rate and that these effects were abolished after destruction of the sympathetic nerve terminals with 6-hydroxydopamine (6-OHDA) pretreatment [11]. This demonstrates that in this model, the effects of PSE on the cardiovascular system are mediated entirely by its indirect actions, and that PSE does not have any direct effects on adrenoceptors on blood vessels or the heart. A similar result was found when using the rat anococcygeal muscle as PSE caused contraction of the muscle but this contractile response to PSE was abolished after destruction of sympathetic nerve terminals with 6-OHDA pretreatment [11].

Cardiovascular Effects of Pseudoephedrine

PSE acts on sympathetic nerve endings supplying all blood vessels and the heart and therefore may cause an increase in arterial blood pressure and an increase in heart rate. However, the blood pressure responses are dose dependent and the changes in blood pressure observed with PSE in over the counter (OTC) doses such as 60mg are minimal and sometimes cannot be detected. In a meta-analysis of 24 clinical trials on 1285 patients, PSE in a wide range of formulations and doses ranging from 40 mg - 180 mg, PSE caused a small but significant increase in mean systolic blood pressure (SBP) of 0.999 mm Hg and an increase in heart rate of 2.83 beats per minute with no effect on diastolic blood pressure (DBP) [12]. Similar results were found in the meta-analysis in patients with controlled hypertension with a mean increase in systolic blood pressure of 1.2 mm Hg [12]. The authors conceded that although minimal cardiovascular effects of PSE were found in the meta-analysis the study could not predict how any individual patient would react to PSE.

Because PSE, like all other nasal decongestants, is a sympathomimetic that causes vasoconstriction there may be a risk of myocardial infarction and stroke, but a study on 1394 patients with myocardial infarction and 1403 patients with stroke, mainly 70 years old or younger, including 3.2% who used decongestants during the three weeks prior to the event, observed no increased risk of myocardial infarction or stroke for patients who had used decongestants [3].

6. Role of Sympathetic Nervous System in Nasal and Cerebral Circulations

PSE acts by releasing noradrenaline from sympathetic nerves and therefore it is

important to understand the effects of sympathetic nerve stimulation on nasal and cerebral blood vessels.

6.1. Sympathetic Innervation of the Nose

Nasal blood vessels are innervated by sympathetic nerves supplied by the cervical sympathetic nerve, and they are relayed to the superior cervical ganglion [13]. The sympathetic innervation of the nose regulates nasal airflow by controlling the congestion of large veins in the nasal epithelium often referred to as 'nasal venous erectile tissue' [14]. The nasal venous erectile tissue has a dense sympathetic innervation and stimulation of the sympathetic nerves causes release of noradrenaline and decongestion of the nose [15]-[19]. The nasal venous erectile tissue is extremely sensitive to adrenaline and studies on the anaesthetised cat have shown that the nose is five times more sensitive than the heart to adrenaline administered intravenously [20]. The extreme sensitivity of nasal venous erectile tissue to sympathomimetics such as adrenaline means that sympathomimetics such as PSE can be used as nasal decongestants at concentrations that have minimal or no effects on the cardiovascular system [12].

The sympathetic innervation to the nasal venous erectile tissue has a resting tone with a continuous vasoconstrictor action, and a section of the sympathetic nerves causes congestion of the nose [21].

6.2. Sympathetic Innervation of Cerebral Blood Vessels

The superficial cerebral arteries are supplied by sympathetic nerves from the cervical sympathetic nerves and these nerves follow the blood vessels until they enter the brain parenchyma [22]. "*Upon their entry into the brain parenchyma, cerebral arteries lose their peripheral nerve supply and, once the Virchow-Robin space has vanished, receive neural input from neurons located within the brain itself, hence the appellation of 'intrinsic innervation' of the brain microcirculation*"

Unlike the nose where blood flow is controlled by sympathetic nervous activity blood flow to the brain is under autoregulation and normal blood flow is controlled by local metabolic activity [23]. Although cerebral blood vessels are innervated by sympathetic nerves, there is conflicting evidence that they control cerebral blood flow under normal conditions [24]. The confusion over the role of sympathetic nerves in controlling human cerebral blood flow is partly due to a lack of human studies and species differences in preclinical experiments. Cerebral perfusion is maintained constant over a wide range of arterial blood pressure and relies on local changes in vascular tone to counter-regulate against changes in systemic arterial blood pressure [23] [25]. In a review on the control of cerebral blood flow, the authors concluded that "*under normal physiological conditions neurogenic control has little influence on cerebral autoregulation as other methods of control* (*vasomotor, chemical, and metabolic*) *are dominant*" [23]. If neurogenic control has little influence on normal cerebral blood flow, then it is unlikely that PSE will influence cerebral blood flow, as the effects of PSE are mediated by noradrenaline

released from sympathetic nerves as described above. Any effects of PSE on cerebral blood flow will be complicated by effects on systemic arterial blood pressure as cerebral blood flow is autoregulated to compensate for any changes in perfusion pressure caused by an increase in blood pressure [25].

7. Efficacy of PSE as a Decongestant

PSE has been used as a nasal decongestant since 1954 and has been available as an OTC product since 1960 [26]. The efficacy of PSE for symptomatic relief of nasal congestion associated with common cold/flu and allergic rhinitis is not questioned by regulatory authorities and there are many studies demonstrating efficacy of PSE alone or in combination with other medicines in these conditions [27]-[31].

PSE-containing medicinal products are available in various oral dosage forms, alone and in combination with antihistamines, analgesics and/or cough suppressants.

PSE-containing medicinal products are mainly indicated for adults and adolescents from the age of 12 years, however, in some member states of the EU, there are some products indicated for children from 6 years of age. PSE is generally not recommended for children under 6 years since the efficacy and safety are not established in this age group.

Its oral adult single dose ranges from 30 to 120 mg as a hydrochloride or sulphate. Most commonly, a maximum intake of 180 mg to 240 mg of PSE daily is recommended by labels.

8. Benefits of Treatment with PSE

Nasal congestion is a common symptom associated with common cold/flu and allergic rhinitis [32]. Approximately 10% - 20% of the global population suffer from allergic rhinitis and upper respiratory tract viral infections such as the common cold/flu, which are the most common human diseases [33]. Viral infections and allergic responses in the nose cause inflammation and dilation of nasal airway blood vessels and swelling of nasal venous erectile tissue to cause nasal obstruction and difficulty breathing through the nose [34] [35].

The major benefit of treatment with PSE in common cold/flu and nasal allergy is decongestion of blood vessels in the nasal airway, and because of the dense sympathetic innervation of these blood vessels and their great sensitivity to sympathomimetics, decongestion occurs with minimal effects on the cardiovascular system [20].

Nasal congestion associated with common cold/flu and nasal allergy can affect quality of life in several different ways: by causing nasal obstruction, by congesting the ostia of the paranasal sinuses, by congesting the pharyngeal orifice of the pharyngotympanic tube (Eustachian tube).

Nasal congestion has a big impact on the quality of life, "*Symptoms, such as nasal congestion, cause high rates of absenteeism as well as* '*presenteeism*,' *where employees are present but underperforming*" [32]. To better understand and ap-

preciate the burden of allergy on the American population, a comprehensive national survey named "Allergies in America" was conducted in January 2006 and survey participants reported a "stuffed-up nose" to be the most bothersome symptom of nasal allergies, and nearly 80% of respondents listed a stuffed-up nose as "extremely" or "moderately" bothersome during a nasal allergy attack [32]. In a telephone survey on American patients with allergic rhinitis Shedden (2005) [36] reported that "*Nasal congestion was the symptom that most adults and children wished to prevent, and it affected most respondents at work or school, had a notable emotional impact, and interfered with their ability to perform daily activities*".

8.1. Benefit of PSE for Treating Nasal Obstruction

Acute and reversible nasal obstruction associated with common cold/flu and nasal allergy has a big impact on quality of life as patients lose the satisfying sensation of cool nasal airflow and are forced to breathe through the mouth [32]. The cool nasal sensation on each inspiration is mediated by cold receptors in the nose [13] [37] [38]. A significant relationship between nasal airway resistance and nasal sensation of airflow has been demonstrated with nasal decongestion causing an increase in nasal sensation of airflow [39]. The cool sensation of normal nasal airflow is not only a pleasant sensation as it has an important role in satisfying the drive to breathe and arousal, and loss or inhibition of this stimulus is disturbing [40]. PSE as described above is an effective nasal decongestant and will provide benefit to the patient by restoring the nasal breathing and sensation of airflow which is compromised by common cold/flu and allergy.

8.2. Benefit of PSE for Treating Sinusitis

The airway inflammation caused by common cold/flu and allergy is often referred to as 'rhinosinusitis' as the paranasal sinuses surrounding the airway are affected by a generalized airway inflammatory response to infection and allergy [41]. The paranasal sinuses comprise large air spaces surrounding the nasal airway, frontal, maxillary ethmoid and sphenoidal sinuses, and they ventilate into the nasal airway by small openings termed "ostia" [42]. The ostia of the paranasal sinuses are surrounded by nasal epithelium containing blood vessels and congestion of these blood vessels during common cold/flu and allergy may obstruct the ventilation and drainage of the sinuses and lead to accumulation of fluid in the sinuses and risk of infection and sinusitis [41] [43]. Sinus pain may be caused by pressure changes in the sealed sinus as gas is absorbed and this results in what is termed "vacuum headache" [44] [45]. Treatment with PSE decongests blood vessels around the ostia of the paranasal sinuses and allows the ostia to open and ventilate and drain the sinuses. PSE is often administered in combination with an analgesic, so the dual effects of decongestion and analgesia relieve the sinus pain.

Sperber *et al.* (2000) studied the effects of an acetaminophen and PSE combination medicine in a double blind placebo controlled study on 430 patients with

sinus pain associated with the common cold and concluded that *"pseudoephedrine plus acetaminophen is effective for relief of symptoms attributable to the paranasal sinuses that may develop early in the course of a cold*" [31]. Laforce *et al.* (2008) studied the effects of guaifenesin plus PSE combination medicine on symptom relief as an adjunctive therapy to antibiotic treatment of acute respiratory infections in 601 patients and concluded that "*guaifenesin/pseudoephedrine shortened time to relief and improved bothersome respiratory symptoms better than placebo, with greatest effects seen for nasal congestion and sinus headache*" [46]. Voelker *et al.* (2018) reported the results of three double blind placebo controlled trials on patients with common cold treated with an aspirin PSE combination medicine, stating that the medicines were effective in controlling symptoms of pain and congestion including nasal/sinus congestion [29].

8.3. Benefit of PSE for Opening the Eustachian Tube

The pharyngeal orifice of the pharyngotympanic tube (Eustachian tube) may become blocked due to inflammation caused by common cold/flu or allergic rhinitis and cause changes in middle ear pressure which are disturbing and often painful [47]-[50]. Studies on the anaesthetized dog have demonstrated that PSE increases the patency of the Eustachian tube [51]. In a placebo controlled study on 22 children with chronic otitis media with effusion who contracted a common cold, a single (60 mg) dose of PSE increased the patency of the Eustachian tube [52]. The effect of PSE in opening the obstructed Eustachian tube may prevent the development of painful pressure changes in the middle ear and could alter the course of the disease by ventilating the middle ear.

After discussing the benefits of therapy with PSE and possible cardiovascular risks, any possible relationship between posterior reversible encephalopathy syndrome and reversible cerebral vasoconstriction syndrome will be discussed.

9. Posterior Reversible Encephalopathy Syndrome (PRES)

Posterior reversible encephalopathy syndrome (PRES) is a "*syndrome of diverse clinical symptoms including visual disturbance, headache, seizures and impaired consciousness. MRI shows oedema, usually involving the posterior subcortical regions. Triggering factors include hypertension, pre-eclampsia/eclampsia, renal failure, cytotoxic agents and autoimmune conditions. The mechanism underlying PRES is not certain, but endothelial dysfunction is implicated*" [53]. **Figure 3** summarises current knowledge about PRES as reviewed by Triplett *et al.* (2022) [53].

PRES has a higher incidence in females and is found in 98% of women with eclampsia and is often associated with hypertension but is also found in patients with normal or even low blood pressure [54].

The mechanisms and pathophysiology of PRES are unknown. However, cerebral endothelial damage and disruption of the blood-brain barrier are known to cause vasogenic oedema [55]. Immunogenic medications, particularly immunosuppressive medicines, are implicated in causing PRES [53] [56]. In a worldwide analysis

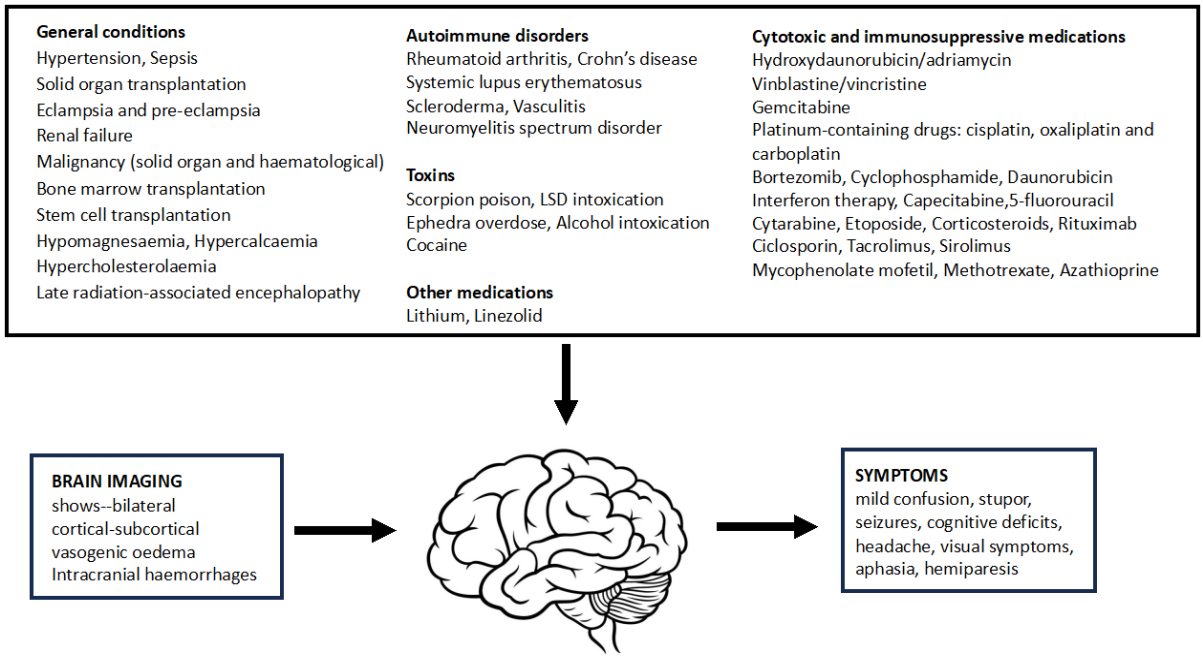

Figure 3. Summary of knowledge on Posterior Reversible Encephalopathy Syndrome (PRES). The diverse list of conditions associated with PRES are listed above and cause a range of non-specific symptoms listed on the right. The diagnosis of PRES relies mainly on brain imaging and the role of pseudoephedrine in causing PRES is unknown.

of medicines associated with PRES using the World Health Organisation pharmacovigilance database Balcerac *et al.* (2023) analysed 3,278 cases of PRES and identified 73 molecules statistically associated with PRES and found that "*the main drug classes involved were antineoplastic and immunomodulating agents and the drugs with the greatest number of cases were tacrolimus*, *cyclosporin*, *bevacizumab*, *methotrexate*, *and vincristine*" [56] and this supports an immunogenic mechanism for PRES. Nasal decongestants such as PSE were not listed amongst 73 medicines potentially associated with PRES based on disproportionality analysis of 3,278 cases reported to VigiBase, the World Health Organization pharmacovigilance database [56].

10. Reversible Cerebral Vasoconstriction Syndrome RCVS

Reversible Cerebral Vasoconstriction Syndrome (RCVS) is associated with sudden severe headache (thunderclap headache) and reversible multifocal cerebral vasoconstriction, and it is more prevalent in women as it often occurs shortly after pregnancy (puerperium) [57]. "*The main precipitating factors described are*: *postpartum state*, *drugs with vasoactive properties*, *such as cocaine*, *marijuana*, *and heroin*, *catecholamine-secreting tumors*, *autoimmune disorders*, *such as systemic vasculitis*, *systemic lupus erythematous*, *antiphospholipid syndrome*, *blood transfusions*, *ginseng*, *sexual intercourse*, *temperature differences* (*baths too hot or too cold*), *air travel*, *Corona Virus Disease* 2019 (*COVID*-19) *infection and medications*". **Figure 4** summarises current knowledge about PRES as reviewed by Ribas *et al.* (2023) [57] and Song *et al.* (2021) [58].

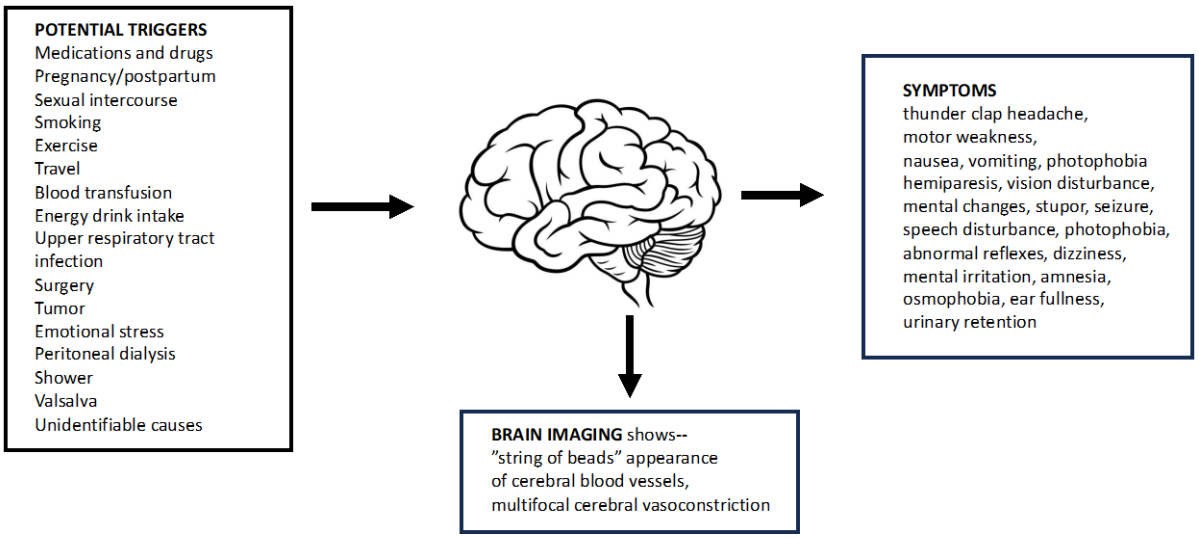

Figure 4. Summary of knowledge on Reversible Cerebral Vasoconstriction Syndrome (RCVS). The diverse list of conditions associated with RCVS is listed on the left and causes a range of non-specific symptoms listed on the right. The diagnosis of RCVS relies mainly on brain imaging and the role of pseudoephedrine in causing RCVS is unknown.

Brain imaging shows that RCVS is accompanied by a "string of beads" appearance of cerebral vessels due to the alternating, simultaneous dilation and constriction, both of which (dilation and constriction) resolve completely within 3 months [59] [60]. The mechanism and pathophysiology of RCVS are unknown but "*unpredictable and transient failure of regulation of cerebral arterial tone with sympathetic overactivity seems to have a role in the development of RCVS*" [60].

11. Benefit-Risk Assessment of PSE

The main benefits of PSE are that it is a nasal decongestant in common cold/flu and allergic rhinitis. As detailed above, the efficacy of PSE as a nasal decongestant is proven and not contested.

This review focuses on the risk of PRES or RCVS associated with the use of PSE. The pathophysiology of PRES and RCVS is unknown, and cases of PRES and RCVS are associated with a very wide range of unrelated conditions, as illustrated in **Figure 3** and **Figure 4**. With such a wide range of conditions associated with PRES and RCVS it is likely that chance association of the conditions with PRES and RCVS is the reason for listing these conditions rather than any causal relationship. This may explain why PSE has been linked to cases of PRES and RCVS even when no other condition is recorded, although, as discussed below, only two cases with complete medical and medication histories can be identified with no other risks apart from taking PSE.

The PRAC Co-rapporteur's updated assessment report on the benefit risk assessment of PSE in relation to PRES and RCVS (2023) [6] identified a total of 34 cases reported through 2023 from the worldwide medical literature and the Eudravigilance database, 18 cases from EU countries, in which "*causal relationship between pseudoephedrine and posterior reversible encephalopathy syndrome*

(*PRES*)/*reversible cerebral vasoconstriction syndrome* (*RCVS*) *is considered at least reasonably possible*."

Of the 34 cases, it was reported by the PRAC Co-rapporteurs that 5 cases had no other risk factor apart from exposure to PSE. However, examination of these cases shows that 3 cases had no information or had clearly incomplete information on medical history and/or concomitant medications, so they were not contributory to an assessment of risk factors (one physician reported case, [4] [61] [62]. For one of these 3 cases, the rapporteur's summary of this case states: "Concomitant medication and patient history not reported, unknown". The second case was an abstract of a poster presentation focusing on radiologic imaging which noted the patient did not have hypertension, but no other past medical history or medication history was described. The third case was a radiologic image-based case report which did not describe any past medical history or medication history. Therefore, these 3 cases should not be considered as scenarios where patients did not have risk factors but rather as incomplete information allowing assessment. Thus, only two remaining cases of the 5 cases considered by the rapporteur had no risk factors reported. Therefore, for nearly all of these cases, other risk factors apart from exposure to pseudoephedrine could be related to the adverse events of PRES/RCVS, and even in the remaining two cases, there could have been unreported risk factors apart from PSE.

It is important when considering the potential for a causal relationship between PSE and PRES/RCVS to take into consideration the population's exposure to PSE.

In order to determine the use of PSE in the EU, data from IQVIA Consumer Health company was obtained for the year 2022 for the number of packs of PSE for mono and combination products which were sold OTC in 2022. In the 20 EU countries and the UK, a total of 72,507,672 packs of pseudoephedrine were sold in 2022.

The 72.5 million packs include tablets and syrups and is an underestimate of the total amount of PSE purchased as it does not include any PSE prescribed by physicians. Data was only available for 20 countries in the EU plus the UK, as the other countries did not have PSE available OTC. In 2023, the population of the 21 countries was 406,813,519. Over the 16-year period (2007-2023) that data for PRES/RCVS was gathered, the sales of OTC pseudoephedrine can be estimated as over 1.16 billion packs of pseudoephedrine and this resulted in only 18 reported cases of PRES/RCVS in the EU (plus UK) with only two of the cases with no other reported risk factors apart from intake of pseudoephedrine. With the small number of PRES/RCVS cases compared to exposure of the population to over 1 billion packs of pseudoephedrine, the risks for developing PRES/RCVS on exposure to pseudoephedrine are likely to be very low.

12. Discussion and Conclusion

Hundreds of different PSE-containing products are taken by millions of people every day across the EU and UK, and it is estimated that more than 70 million

packs of PSE products are taken every year.

PSE has sympathomimetic properties and, therefore, has the potential to cause vasoconstriction and tachycardia. However, the low OTC doses of PSE have little effect on the cardiovascular system.

Possible adverse effects of PSE in causing PRES and RCVS have recently been discussed by regulatory authorities, and warnings and contraindications have been added to patient instructions for the use of PSE products. PRES and RCVS are rare conditions of unknown etiology, and the number of cases involving the use of PSE and a possible link to the onset of PRES and RCVS are small, and it is difficult to link PSE as a definite cause of PRES and RCVS.

The opinion of the reviewer is that any causal relationship between the use of PSE and adverse events of PRES/RCVS is unlikely and that the benefits outlined in this review of PSE-containing medicines outweigh any risk associated with the onset of PRES and RCVS.

13. Statements and Declarations

The author has no competing interests and has no financial or other interests in any pharmaceutical company. The author will receive payment from the Association of the European Self-Care Industry (AESGP) for time spent in the preparation of this manuscript, and this payment will also fund any publication charges for open access. The opinions expressed in this review are solely those of the author.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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