Medicines Adverse Reactions Committee

Meeting date	11/09/2025	Agenda item	3.2.3
Title	**Risk of seizures after use of beta-2 agonists in patients with convulsive disorders**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice

Active ingredient	**Product name**	**Sponsor**
Formoterol	Oxis Turbuhaler	AstraZeneca Limited
Formoterol + Budesonide	Symbicort Turbuhaler	AstraZeneca Limited
	Vannair Aerosol inhaler	AstraZeneca Limited
	DuoResp Spiromax Powder for inhalation	Teva Pharma (NZ) Limited
Formoterol + Budesonide + Glycopyrronium	Breztri Aerosphere Aerosol inhaler	AstraZeneca Limited
Indacaterol	Onbrez Breezhaler	Novartis New Zealand Limited
Indacaterol + Glycopyrronium	Ultibro Breezhaler	Novartis New Zealand Limited
Olodaterol + Tiotropium	Spiolto Respimat Solution for inhalation	Boehringer Ingelheim (NZ) Limited
Salbutamol	Asthalin Solution for inhalation	GlaxoSmithKline NZ Limited
	Ventolin inhaler, Solution for injection, Syrup	GlaxoSmithKline NZ Limited
	SalAir Aerosol inhaler	REX Medical Ltd
Salbutamol + Ipratropium	Duolin Aerosol inhaler, Solution for inhalation	REX Medical Ltd
Salmeterol	Serevent Inhaler Aerosol inhaler, Accuhaler	GlaxoSmithKline NZ Limited
	Meterol Aerosol inhaler	REX Medical Ltd
Salmeterol + Fluticasone propionate	Seretide Aerosol inhaler, Accuhaler	GlaxoSmithKline NZ Limited
	Rexair Aerosol inhaler	REX Medical Ltd
Terbutaline	Bricanyl Turbuhaler	AstraZeneca Limited
Vilanterol + Fluticasone furoate	Breo™ Ellipta	GlaxoSmithKline NZ Limited
Vilanterol + Umeclidinium	Anoro Ellipta	GlaxoSmithKline NZ Limited
Vilanterol + Umeclidinium + Fluticasone furoate	Trelegy Ellipta Powder for inhalation	GlaxoSmithKline NZ Limited

PHARMAC funding	Most of the listed products are fully funded, except for the Oxis Turbuhaler and Ventolin inhaler which are only partially funded
Previous MARC meetings	None

Prescriber Update	Not applicable
Classification	Prescription medicine
Usage data	Funded community **dispensings** in 2023 (see also section 2.6, Usage): • 1,261,431 Salbutamol • 990,801 Formoterol + Budesonide • 384,053 Salmeterol + Fluticasone • 83,272 Vilanterol + Umeclidinium
Advice sought	**The Committee is asked to advise:** • On the strength of the evidence that some or all β2-agonists may trigger seizures in patients with epilepsy. • Whether the data sheets for some, or all, medicines containing β2-agonists should include warnings regarding use in patients with convulsive disorders. • Whether this topic requires further communication other than MARC's Remarks in Prescriber Update.

Table of Contents

1 PURPOSE 4
2 BACKGROUND 4
2.1 Beta-2 adrenergic agonists (β2-agonists) 4
2.2 Indications for use of β2-agonists 4
2.3 Convulsive disorder 4
2.4 Data sheets 6
2.5 Usage 8
3 SCIENTIFIC INFORMATION 8
3.1 Published literature 8
3.1.1 Uysalol M et al., 2022. Is Seizure an Adverse Effect of Salbutamol in the Pediatric Population? [15] 9
3.1.2 Chen J et al., 2018. *In utero* beta-2-adrenergic agonists exposure and risk of epilepsy: A Danish nationwide population-based cohort study (Annex 1) [16] 11
3.1.3 Singh A et al., 2018. Aggravation of Seizure after Combined Nebulisation with Albuterol and Ipratropium Bromide [17] 12
3.1.4 Ozdemir E, 2024. Adrenergic receptor system as a pharmacological target in the treatment of epilepsy (Review) [14] 12
3.1.5 Biagioni F et al., 2023. Noradrenaline and Seizures: A Perspective on the Role of Adrenergic Receptors in Limbic Seizures [23] 13
3.2 New Zealand Adverse Drug Reaction (ADR) Reports 14
3.3 International ADR Reports 16
[redacted] 16
[redacted] 17
4 DISCUSSION AND CONCLUSIONS 17
5 ADVICE SOUGHT 18
6 ANNEXES 18
7 REFERENCES 18

1 PURPOSE

Inhaled selective beta-2 adrenergic agonists (β2-agonists) are widely used in the management of respiratory conditions such as bronchial asthma, chronic obstructive pulmonary disease (COPD), and prevention of premature labour, when given intravenously [1].

This report reviews the possible seizure risk associated with β2-agonists use in patients with convulsive disorders, following another regulatory request to include the warning below in section 4.4 of Anoro Ellipta:

> *"Anoro Ellipta should be used with caution in patients with convulsive disorders or thyrotoxicosis, and in patients who are unusually responsive to beta2-adrenergic agonists."*

This warning is not currently included in the New Zealand Anoro Ellipta data sheet, and the [redacted]

This paper only discusses the risk of use in patients with convulsive disorders. Since beta blockers are a mainstay of treatment for thyrotoxicosis, a warning for patients with thyrotoxicosis regarding beta agonist use is clear cut. Medsafe intends to request a data sheet update from all relevant sponsors regarding this warning. Medsafe considers that the phrase "patients who are unusually responsive to beta2-adrenergic agonists" is ambiguous and lacks sufficient detail to conduct an extensive safety review. Therefore, this report focuses specifically on the proposed warning for patients with convulsive disorders.

2 BACKGROUND

2.1 Beta-2 adrenergic agonists (β2-agonists)

Selective β2-agonists are indicated for treatment of asthma and COPD, they work by relaxing the muscles around the airways in the lungs, allowing air to flow more easily. While these agents primarily target β2 receptors in the lungs to minimise side effects elsewhere, they can still affect other receptors, which is why they are also used in other situations like preventing miscarriage or lowering potassium levels in the blood. [1, 2]

β2-agonists are classified based on how their duration of action: short-acting β2-agonists (SABAs) work quickly but for a short period, while long-acting β2-agonists (LABAs) take longer to work but have an effect for a longer period. While β2-agonists may be prescribed on their own (monotherapy) recent guidance is to only use them in combination with inhaled corticosteroids. [2][3]

2.2 Indications for use of β2-agonists

Mild to moderate asthma symptoms usually respond rapidly to inhalation of a SABA, such as salbutamol or terbutaline [2]. SABAs have also been used for short-term relief of breathlessness in patients with COPD [4].

LABAs (e.g., formoterol, salmeterol) are indicated for the maintenance treatment of both asthma (in combination with a corticosteroid) and COPD [3, 4].

Salbutamol injection is also indicated for the management of uncomplicated premature labour, with use limited to a maximum duration of 48 hours [5, 6]. At therapeutic dose, selective β2-agonists act on the receptors in the uterus and suppress contractions associated with premature labour [6].

2.3 Convulsive disorder

Convulsive disorders, commonly referred to as seizures, result from abnormal electrical activity in the brain. Epilepsy is the most common cause of recurrent seizures.

The International League Against Epilepsy (ILAE), classifies epileptic seizures into focal generalised, unknown, and unclassified types with further subtypes based on clinical features [7]. However, in lay terms, 'convulsion'

typically refers to a generalised tonic-clonic seizure, which involves widespread muscle contractions and uncontrollable shaking of the body [8].

It is estimated that approximately 1 to 2 in every 100 people in New Zealand develop epilepsy at some point in their lives [9]. A prospective, population-wide study found that 5.49 per 1,000 people in New Zealand live with active epilepsy [10]. Among this population, the annual incidence of sudden unexpected death in epilepsy (SUDEP) was 1.93 per 1,000 individuals [10].

Several studies have reported significant increases in plasma catecholamines, particularly epinephrine (also known as adrenaline) and norepinephrine (noradrenaline), following seizures [11-13]. In a study by Nass et al. (2019), cardiac stress was investigated in patients with refractory epilepsy after generalised convulsive seizures using cardiac biomarkers and ECG monitoring [11]. The researchers found that postictal catecholamine levels, including dopamine, were elevated more than two-fold, and higher dopamine levels were associated with increased cardiac troponin, suggesting a potential link between catecholamine surges and subclinical cardiac injury [11]. Similarly, a multicentre study by Rani et al. (2020) demonstrated that postictal levels of epinephrine, norepinephrine, and dopamine were significantly elevated after both convulsive and non-convulsive seizures, with epinephrine increasing up to five-fold following generalised convulsive seizures [13].

Norepinephrine is thought to interact with multiple neurotransmitter systems, particularly GABA and glutamate, and plays a role in modulating voltage-gated calcium and potassium channels [14]. Interestingly, both elevated and reduced levels of norepinephrine in the brain have been associated with increased seizure risk, underscoring the adrenergic system as a potential therapeutic target in epilepsy management [14].

Comments:

Plasma catecholamines, particularly epinephrine and norepinephrine, are believed to rise significantly following seizures. β2-agonists mimic the physiological effects of endogenous catecholamines, potentially influencing the course of a seizure.

2.4 Data sheets

Table 1 summarises whether the safety warnings related to convulsive disorders are included in product information from different countries. Table 2 summarises the warning text included in the indacaterol and olodaterol data sheets.

Table 1: Summary of safety warnings for β2-agonists in patients with convulsive disorders in different countries

Medicine	New Zealand	Australia	UK	US
Formoterol	Not included	Not included	Not included	Included
Formoterol + Budesonide	Not included	Not included	Not included	Included
Formoterol + Budesonide + Glycopyrronium	Not included	Not included	Not included	Included
Indacaterol	Included	Included	Included	No information identified
Indacaterol + Glycopyrronium	Included	Included	Included	No information identified
Olodaterol + Tiotropium	Included	Included	Included	Included
Salbutamol	Not included	Not included	Not included	Included
Salbutamol + Ipratropium	Not included	No information identified	Not included	Included
Salmeterol	Not included	Not included	Not included	Included
Salmeterol + Fluticasone propionate	Not included	Not included	Not included	Included
Terbutaline	Not included	Not included	Not included	Included
Vilanterol + Fluticasone furoate	Not included	Included	Included	Included
Vilanterol + Umeclidinium	Not included	Not included	Included	Included
Vilanterol + Umeclidinium + Fluticasone furoate	Not included	Not included	Included	Included

A more detailed comparison of the warning listed in the New Zealand data sheets for β2-agonists is provided in Table 2.

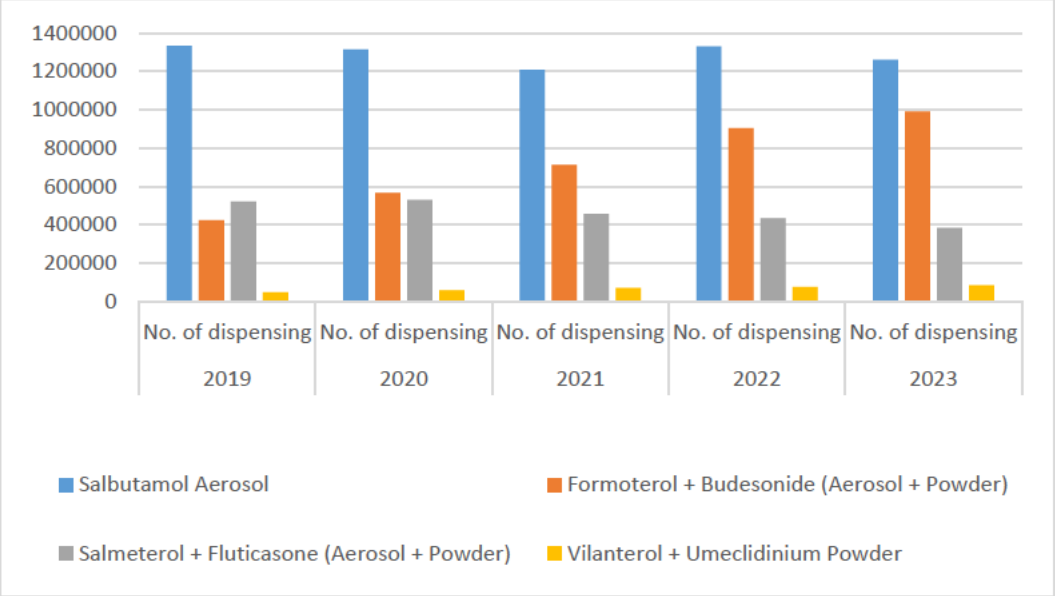
Table 2: Safety warning wordings in New Zealand data sheets for β2-agonists

Medicine	Wording on warnings
Indacaterol (Onbrez)	Although no clinically relevant effect on the cardiovascular system is usually seen after the administration of ONBREZ® at the recommended doses, as with other β2-adrenergic agonists, ONBREZ®, should be used with caution in patients with cardiovascular disorders (coronary artery disease, acute myocardial infarction, cardiac arrhythmias hypertension) in patients with convulsive disorders or thyrotoxicosis, and in patients who are unusually responsive to β2-adrenergic agonists.
Indacaterol + Glycopyrronium (Ultibro)	Although no clinically relevant effect on the cardiovascular system is usually seen after the administration of ULTIBRO BREEZHALER 110/50 at the recommended dose, as with other compounds containing a beta2-adrenergic agonist, ULTIBRO BREEZHALER 110/50 should be used with caution in patients with cardiovascular disorders (coronary artery disease, acute myocardial infarction, cardiac arrhythmias, hypertension), in patients with convulsive disorders or thyrotoxicosis, and in patients who are unusually responsive to beta2-adrenergic agonists.
Olodaterol + Tiotropium (Spiolto Respimat)	SPIOLTO RESPIMAT contains a long acting beta2-adrenergic agonist. Long acting beta2-adrenergic agonists should be administered with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, hypertrophic obstructive cardiomyopathy and hypertension; in patients with convulsive disorders or thyrotoxicosis, in patients with known or suspected prolongation of the QT interval; and in patients who are unusually responsive to sympathomimetic amines.

2.5 Usage

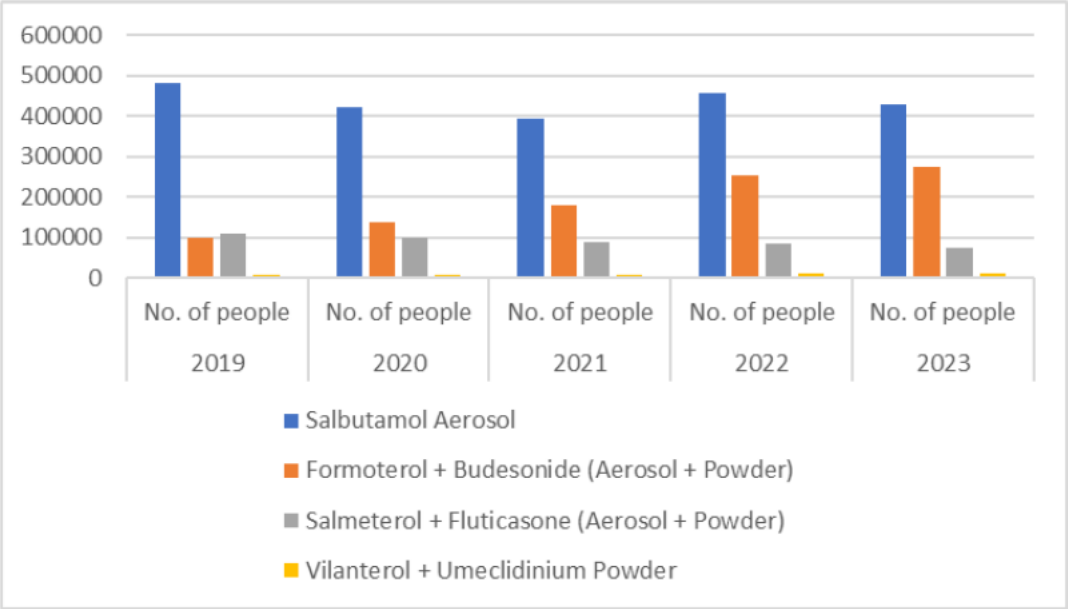
Usage data for β2-agonists dispensed in the community is shown in Figure 1 and Figure 2.

Figure 1: Dispensing trends of β2-agonist in New Zealand from 2019 to 2023 - number of dispensing



Source: Te Whatu Ora Pharmaceutical Data Web Tool (accessed 19 May 2025)

Figure 2: Dispensing trends of β2-agonist in New Zealand from 2019 to 2023 - number of individuals treated



Source: Te Whatu Ora Pharmaceutical Data Web Tool (accessed 19 May 2025)

3 SCIENTIFIC INFORMATION

3.1 Published literature

A literature search conducted via PubMed from 19 May 2015 to 19 May 2025 identified 99 articles. Of these, four were considered relevant: two retrospective cohort studies and two perspective animal studies discussing

potential mechanisms. Additionally, one case report was identified by the Ministry of Health's reference librarian.

Search details used: ((beta 2 agonist) OR (formoterol) OR (indacaterol) OR (olodaterol) OR (salbutamol) OR (salmeterol) OR (terbutaline) OR (vilanterol) OR (albuterol)) AND ((epilepsy) OR (seizure) OR (convulsion disorder))

3.1.1 Uysalol M et al., 2022. Is Seizure an Adverse Effect of Salbutamol in the Pediatric Population? [15]

Purpose: Authors conducted a retrospective cohort study to investigate whether salbutamol triggers seizures in patients with epilepsy and asthma.

Study type: A retrospective cohort study.

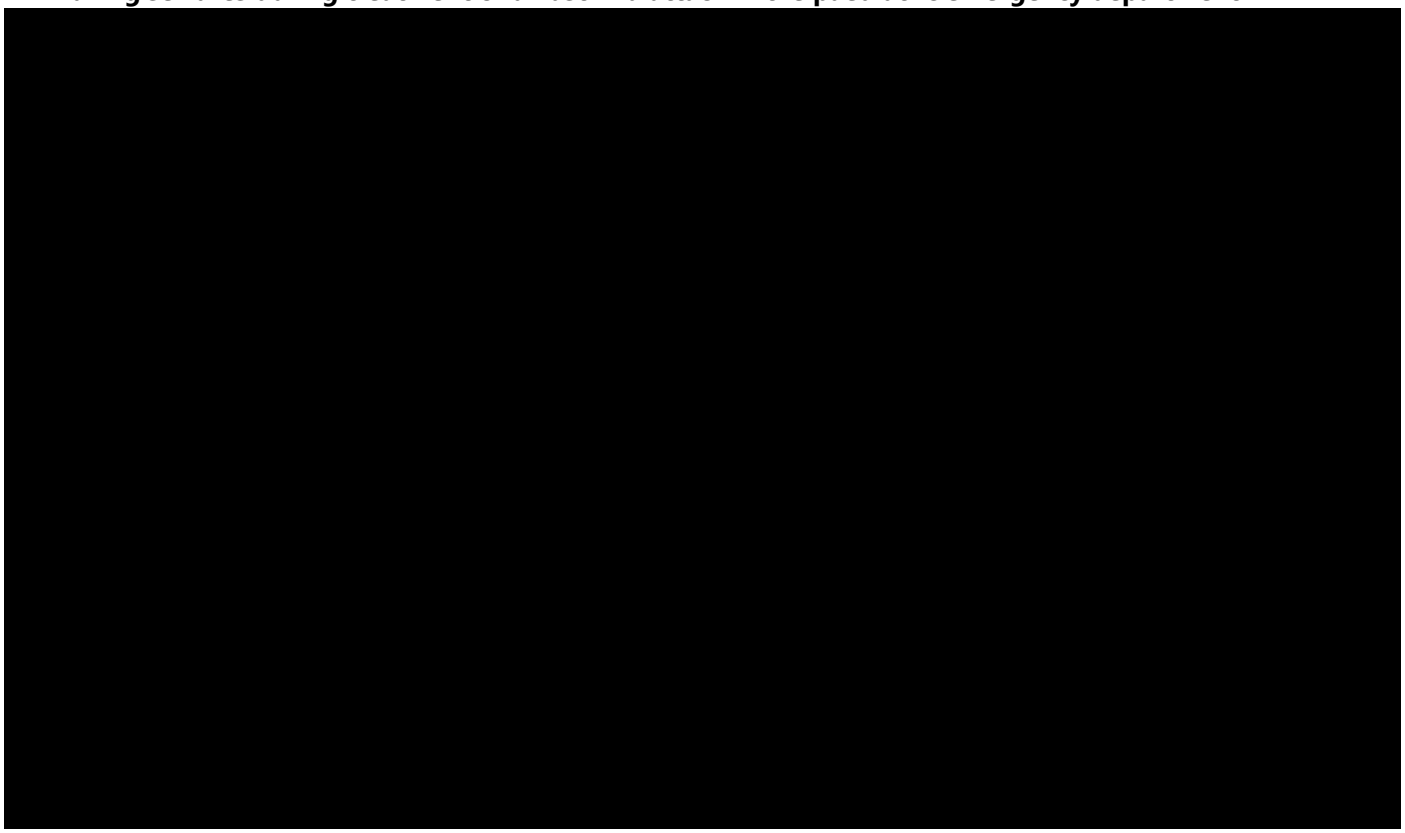
Method: A retrospective evaluation was conducted on patients aged 2 to 18 years with a history of both epilepsy and asthma who were admitted to the paediatric emergency department (PED) of a university hospital due to respiratory distress between January to December 2016. Inclusion criteria included age between 2 to 18 years, a prior diagnosis of epilepsy and asthma, and admission to the PED for an asthma attack. Data collected included demographic characteristics, history of salbutamol use, any reported increase in convulsions associated with salbutamol use, and the occurrence of seizures following salbutamol administration during hospitalisation. First-line treatment for asthma attacks consisted of short-acting β2-agonists, ipratropium bromide, and corticosteroids. Seizure activity following treatment was also documented.

Results: The authors collected and evaluated the medical records of 276 patients. Demographic and clinical characteristics of patients with epilepsy were grouped and compared based on the presence or absence of seizures during their visit to the PED, as shown in Table 3. While age and sex were similar between the two groups, the seizure group had a longer duration of their diagnosis of both epilepsy and asthma. Additionally, patients in the seizure group had a higher number of admissions of epileptic seizures to the PED. The frequencies of seizures occurring during asthma attacks and during historical salbutamol treatment were also greater in the seizure group. Patients in the seizure group were using a greater number of antiepileptic medicines and had a higher prevalence of a history of status epilepticus. Patients with uncontrolled or severe asthma experienced significantly more frequent seizures during asthma attack treatment in the PED. The seizure group exhibited a significantly higher rate of nonresponse to first-line treatment.

The frequency of drug-resistant epilepsy was significantly higher among patients who experienced seizures during asthma treatment compared to those who did not (85% vs 65%, respectively).

Among those not using their indicated salbutamol, 58 patients (33.3%) reported avoiding it due to a history of seizures associated with its use. Moreover, 116 patients (66.7%) were not using salbutamol despite having no history of seizures associated with its use. Notably, patients who used salbutamol had a significantly lower rate of emergency department admissions due to epileptic seizures.

Table 3: Demographics and clinical characteristics of patients with epilepsy grouped according to having seizures during treatment of an asthma attack in the paediatric emergency department



After adjusting for age and sex, independent predictors of experiencing a seizure during an asthma attack included the duration of asthma and epilepsy diagnoses, level of asthma control, and the severity of the asthma attack in the PED, as detailed in Table 4.

Table 4: Age- and sex-adjusted independent correlates of having a seizure during an asthma attack

Conclusion: The duration of asthma diagnosis, presence of uncontrolled asthma, and severity of asthma attacks in the emergency department were associated with an increased risk of seizures during salbutamol use. In cases of severe asthma, children may be particularly vulnerable to seizures. Overall, the authors concluded that patients using salbutamol had a lower risk of epileptic seizures compared to those who did not. They also emphasized the importance of timely diagnosis and treatment of asthma based on evidence-based guidelines. The study did not address its limitations or potential confounding factors.

Comments:
This retrospective cohort study investigated whether salbutamol triggers seizures in patients with epilepsy and asthma. The findings indicated that the severity and level of control of the underlying conditions, namely asthma and epilepsy, had a greater influence on seizure risk than salbutamol treatment itself.

Notably, the authors reported that among the 37 patients with a history of status epilepticus, 36 did not experience seizures during asthma attack treatment. However, this statement appears to contradict the data presented in Table 3, suggesting a possible discrepancy in either the narrative or the dataset.

Given the retrospective nature of the study, causality cannot be established. Nonetheless, the findings challenge the assumption of a direct causal relationship between salbutamol and seizures, instead highlighting the potential influence of underlying disease severity. The authors appropriately acknowledge that these results should be validated in studies with larger patient populations.

While the study underscores the importance of β2-agonists in managing severe asthma exacerbations, it does not definitively rule out the possibility that salbutamol may have seizure-triggering properties in certain patients.

3.1.2 Chen J et al., 2018. *In utero* beta-2-adrenergic agonists exposure and risk of epilepsy: A Danish nationwide population-based cohort study (Annex 1) [16]

Purpose: To examine the association between maternal use of β2-agonists and the risk of epilepsy in offspring.

Study type: Retrospective cohort study.

Method: A nationwide retrospective cohort study was conducted using data from the Danish national registries of all singleton live births from 1 January 1998 through to 31 December 2008. Exclusion criteria included births with missing maternal personal identification numbers, missing parity information, or gestational age ≤23 weeks or ≥45 weeks. The study compared children born to mothers who used β2-agonists during pregnancy (30 days before the beginning of pregnancy until delivery) with those unexposed, with the primary outcome being a diagnosis of epilepsy in the offspring.

Cox proportional hazards regression was used to estimate hazard ratios, adjusting for a range of parental and child-related factors. To address potential confounding by indication, the exposure window was extended to include the two years preceding pregnancy, and analyses were stratified by maternal asthma status, including trimester-specific exposure assessments.

Results: Children exposed to β2-agonists during pregnancy had a 1.24-fold increased risk of epilepsy (HR =1.24; 95% CI: 1.12-1.38). Compared to unexposed children, the risk was elevated with maternal β2-agonists use only before pregnancy (HR =1.11), only during pregnancy (HR =1.28), and both before and during pregnancy (HR =1.23). The increased risk was significant only with first- (HR =1.33) or second trimester (HR =1.35) exposure, not the third.

Conclusion: The authors concluded that in utero exposure to β2-agonists, particularly during the first or second trimesters, may be associated with an increased risk of epilepsy. While confounding by indication is possible, a direct causal link cannot be ruled out.

Comments**:**

This retrospective cohort study used Danish national registry data to compare children born to mothers who used β2-agonists during pregnancy with those unexposed, with the primary outcome being a diagnosis of epilepsy in the offspring.

Notably, the exposed and unexposed groups were adjusted by various factors, including maternal employment status. However, the rationale for including this variable in relation to the development of epilepsy in offspring is unclear. In contrast, a well-established risk factor, family history of epilepsy, was not considered as a potential confounder, which may limit the validity of the findings.

Given the retrospective design and its potential limitations, causality could not be established. Nevertheless, the authors suggested a potential association between in utero exposure to β2-agonists, particularly during the first or second trimesters, and an increased risk of epilepsy.

3.1.3 Singh A et al., 2018. Aggravation of Seizure after Combined Nebulisation with Albuterol and Ipratropium Bromide [17]

This case report involves a 65-year-old male who was hospitalised with type II respiratory failure. Five minutes after initiating nebulised therapy with salbuterol (albuterol in the US) and ipratropium bromide, the patient experienced two episodes of generalised tonic clonic seizures. The temporal association suggests a possible link between the onset of seizures and the administration of the salbutamol/ipratropium bromide combination. Based on this observation, the author suggests that this combination therapy should be used with caution, or potentially avoided, in elderly patients with a known history of seizures.

3.1.4 Ozdemir E, 2024. Adrenergic receptor system as a pharmacological target in the treatment of epilepsy (Review) [14]

Purpose: The role of norepinephrine and the adrenergic receptor (AR) system is thought to play a role in the pathophysiology of epileptic seizures. This review focuses on norepinephrine and ARs involved in epileptic seizure formation and discusses therapeutic approaches.

Study type: Perspective review.

Method: Not applicable.

Results: Beta-adrenergic receptors (β-ARs) are low-affinity receptors for norepinephrine. They can be activated during periods of high norepinephrine release. Prolonged stimulation of β-ARs can lead to receptor desensitisation and reduced responsiveness. Administration of β2-agonists to mice has been found to reduce pentylenetetrazol-induced seizures, and salbutamol has demonstrated anti-epileptic effects in mouse models of maximal electroshock-induced seizures.

The role of β-ARs in epileptic seizures remains largely unclear, with rodent studies reporting conflicting outcomes. One study suggests that β-blockers such as propranolol may inhibit anticonvulsant effects of norepinephrine, potentially increasing seizure susceptibility [18]. In contrast, other studies have shown that propranolol exhibit anticonvulsant properties, likely through sodium channel blockade [19-21]. Additionally, timolol has been found to selectively block proconvulsant activity, indicating a possible protective role [22].

While an increase in seizure activity might be expected with the use of β-blockers, several studies have shown that β-blockers can exert anticonvulsant effects in various animal models. For example, the non-selective β-AR antagonist propranolol demonstrates anticonvulsant properties, likely through sodium channel blockade - a mechanism also proposed for the β2-agonist clenbuterol. Additionally, stimulation of β-ARs has been shown to reduce limbic seizures by increasing dopamine levels in the hippocampus, whereas the β-blocker timolol has been found to inhibit proconvulsant activity. These findings suggest that multiple mechanisms may underlie seizure modulation in animal models and highlight the potential role of β2-agonists in mediating the anticonvulsant effects of norepinephrine.

Figure 3: The proposed mechanism of action of the adrenergic receptor system in epileptic seizures
Figure 3 illustrates that the release of norepinephrine in the hippocampus can activate multiple receptor types, including β2-adrenergic receptors. Activation of β2-adrenergic receptors may result in increased dopamine levels within the hippocampus and may contribute to the suppression of epileptic seizures.

Conclusion: The effects of norepinephrine on seizures vary depending on the subtype of adrenergic receptor activated and the specific brain region involved. Norepinephrine can exert both anticonvulsant and proconvulsant effects. Its role in seizure modulation may involve interactions with various neurotransmitter systems, particularly GABA and glutamate, as well as the regulation of voltage-gated calcium and potassium channels. In conditions of heightened seizure susceptibility (e.g., during stress, when norepinephrine levels are elevated) its ability to suppress seizures may become impaired. Several studies have shown that both elevated and reduced levels of norepinephrine in the brain may increase susceptibility to seizures.

Comments**:**

This perspective review explored the role of the adrenergic system in epilepsy and the therapeutic potential of AR agonists.

These findings suggest that multiple mechanisms may underlie seizure modulation in animal models and highlight the potential role of β2-agonists in mediating the anticonvulsant effects of norepinephrine.

3.1.5 Biagioni F et al., 2023. Noradrenaline and Seizures: A Perspective on the Role of Adrenergic Receptors in Limbic Seizures [23]

Purpose: To explore the potential role of the β2-adrenergic receptor as an anticonvulsant target in the anterior piriform cortex, specifically the area tempestas.

Study type: Perspective study.

Method: The analysis is based on current literature (rodent studies) regarding the role of norepinephrine in limbic seizures and autophagy. It is supported by preliminary data from experiments involving microinfusion of either a β2-agonists (salbutamol) or antagonist (butoxamine) into the area tempestas, administered five minutes prior to bicuculline (a selective GABA-A receptor antagonist).

Results: Figure 4 reports the percentage of rats undergoing seizures following various treatments in a single experiment (N=8 rats per group). Seizures occurred in 100% of rats in the Bic, Butox+Bic, and Butox+Salbut+Bic groups, in 37.5% of rats in the Salbut+Bic group, and in none of the rats in the Salbut or Butox groups.

Pre-treatment with the β2-agonists salbutamol effectively prevented focal, serial seizures induced by bicuculline infusion. This protective effect was abolished when rats were pre-treated with the selective β2-antagonist butoxamine. Notably, butoxamine not only blocked salbutamol's anticonvulsant action but also increased seizure frequency and severity when administered prior to bicuculline or to the combination of salbutamol and bicuculline. These findings highlight a critical role for β2-adrenergic receptors in the area tempestas in modulating seizure activity.

Figure 4: Seizure occurrence in rats micro-infused bicuculine within area tempestas after pre-treatment with saline, β2-agonists, or antagonists. Bic: saline, Salbut: salbutamol, Butox: butoxamine

Conclusion: The anticonvulsant action of norepinephrine via β2-adrenergic receptors may be linked to the activation of the autophagy pathway. Recent studies, along with their findings, suggest that β2-adrenergic receptor stimulation not only promotes autophagy but also suppresses seizure activity locally within the area tempestas. Further investigation is warranted to elucidate the mechanisms connecting β2-adrenergic receptor activation, autophagy, and seizure modulation.

Comments**:**

This perspective review analysed literature regarding the role of norepinephrine in limbic seizures and autophagy. Studies in rodents found that β2-agonists (salbutamol) may have a positive effect on seizure frequency and duration.

However, the clinical significance of these findings in humans is unknown.

The authors conclude that further investigation is needed to clarify the specific roles of all adrenergic receptor subtypes in modulating seizures originating from the brain region called tempestas (basal forebrain).

3.2 New Zealand Adverse Drug Reaction (ADR) Reports

As of 6 June 2025, the New Zealand Database contains 1238 reports in which a β2-agonist containing medicine was identified as the suspect medicine. Among these, 5 reports were classified under High-Level Term Group (HLGT) 'Seizures (incl subtypes) (see Table 5).

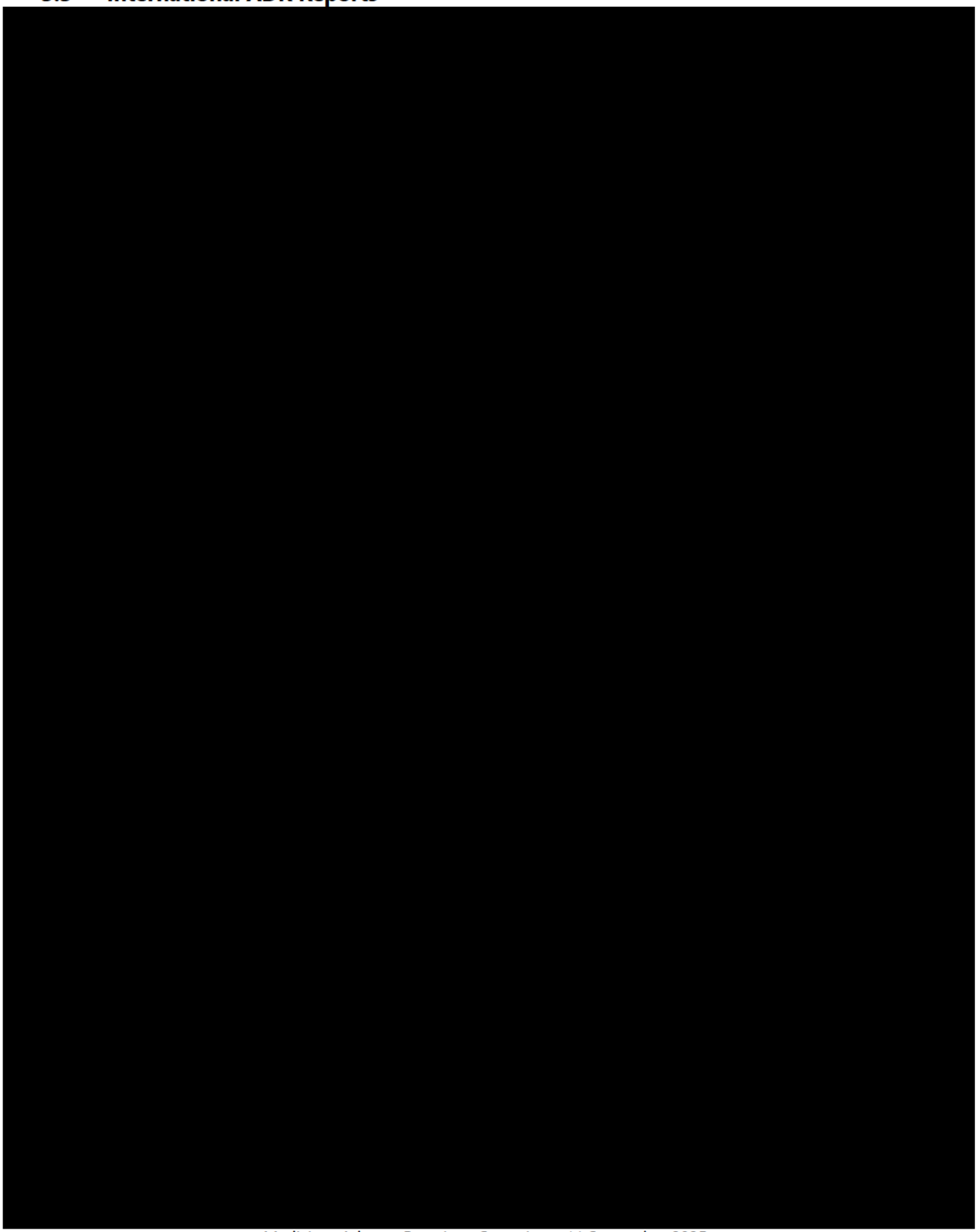
Table 5 presents New Zealand ADR reports involving β2-agonists that are classified under the MedDRA HLGT 'Seizures (incl subtypes)' as of 6 June 2025.

Table 5: β2-agonist ADR reports classified under the MedDRA HLGT 'Seizures (incl subtypes)'

Report ID	[redacted]	Age (years)/age group and sex	Suspect(s)	[redacted]	Reaction (Preferred Term)	[redacted]
032613	[redacted]	30, female	Salbutamol inhaler	[redacted]	Seizure	[redacted]
037416	[redacted]	10, male	Terbutaline turbuhaler	[redacted]	Seizure	[redacted]
039253	[redacted]	45, male	Salbutamol	[redacted]	Generalised tonic-clonic seizure	[redacted]
056199	[redacted]	73, male	Budesonide + formoterol turbuhaler	[redacted]	Seizure	[redacted]
NZ-Medsafe-152769	[redacted]	Adult, female	Budesonide + formoterol turbuhaler	[redacted]	Seizure	[redacted]

Source: New Zealand Pharmacovigilance Database. Suspected adverse reactions to medicines (accessed 16 June 2025)

3.3 International ADR Reports



[redacted]

3.3.2 [redacted]

[redacted]

3.3.2.1 [redacted]

[redacted]

4 DISCUSSION AND CONCLUSIONS

The current evidence suggests that norepinephrine may exert both anticonvulsant and proconvulsant effects. Selectively β2 adrenergic receptors, mimic the effects of endogenous catecholamines (epinephrine, norepinephrine) meaning that there is a theoretical potential for them to influence seizure frequency [25, 26]. However, it is unclear whether β2-agonists have any clinical effect on seizure frequency.

A literature review did not identify any strong or consistent indication of an increase in seizure in those with pre-existing convulsive disorder using beta agonists. There are however case reports in the literature and pharmacovigilance databases.

A review of product information highlighted discrepancies across the class of β2-agonists, where newer medicines included a warning, but older medicines did not.

The Medicines Adverse Reactions Committee are asked to provide advice on whether any action is required.

5 ADVICE SOUGHT

The Committee is asked to advise:

- On the strength of the evidence that some or all β2-agonists may trigger seizures in patients with epilepsy.
- Whether the data sheets for some, or all, medicines containing β2-agonists should include warnings regarding use in patients with convulsive disorders.
- Whether this topic requires further communication other than MARC's Remarks in Prescriber Update.

6 ANNEXES

Annex 1 - In utero beta-2-adrenergic agonists exposure and risk of epilepsy: A Danish nationwide population-based cohort study. Chen J et al., 2018.

7 REFERENCES

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