Research Square

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A disproportionality analysis of dual bronchodilators based on the FAERS

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Abstract

Objective

To detect adverse event (AE) signals for dual bronchodilators using the Food and Drug Administration(FDA) Adverse Event Reporting System (FAERS), assess their potential safety risks, and inform pharmacovigilance.

Methods

AE reports pertaining to dual bronchodilators were retrieved from the FAERS for the period covering the fourth quarter of 2013 through the fourth quarter of 2025. Signal detection was subsequently conducted using both the Reporting Odds Ratio (ROR) and the Multi-Item Gamma Poisson Shrinker (MGPS) method.

Results

From the FAERS database, the numbers of AE reports with umeclidinium/vilanterol, indacaterol/glycopyrronium, tiotropium/olodaterol, glycopyrronium/formoterol, and aclidinium/formoterol as primary suspected drugs were 1,674, 674, 572, 102, and 52, respectively; the corresponding numbers of detected AE signals were 140, 111, 64, 30, and 10; and the numbers of involved system organ classes (SOCs) were 19, 16, 15, 12, and 7, respectively.

Conclusion

The AEs of dual bronchodilators were predominantly observed in the SOCs of respiratory, thoracic and mediastinal disorders, cardiac disorders, and infections and infestations, etc. The distribution of AE signals and serious adverse events(SAEs) varied across the five drugs. Accordingly, individualized drug selection is advised in clinical practice, with special attention to early risk monitoring in elderly patients and those with compromised baseline cardiopulmonary function.

1 Introduction

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable chronic inflammatory airway disease [1, 2], characterized by persistent airflow limitation and respiratory symptoms [2], and associated with high morbidity, disability, and mortality [3]. In recent years, dual bronchodilator therapy—i.e., fixed-dose combinations of a long-acting β_2-agonist (LABA) and a long-acting muscarinic antagonist (LAMA)—has emerged as an important treatment option for COPD [4]. According to the 2026 Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy report, the LAMA/LABA combination is the only initial therapy recommended for Group B patients (those with more symptoms and no moderate or severe exacerbations in the preceding year) and the preferred choice for Group E patients (those with one or more moderate or severe exacerbations in the past year) [5]. Compared with LAMA or LABA monotherapy, LAMA/LABA significantly improves lung function, dyspnea scores, quality of life, and nighttime and morning symptoms, while also reducing exacerbations [6, 7]. Relative to LABA/inhaled corticosteroids (ICS), LAMA/LABA is superior or at least comparable in improving lung function, and is non-inferior or even superior in preventing exacerbations, while avoiding ICS-associated risks such as pneumonia [6, 7]. Currently, five LAMA/LABA fixed-dose combinations are marketed: umeclidinium bromide/vilanterol, indacaterol/glycopyrronium, tiotropium bromide/olodaterol glycopyrronium bromide/formoterol fumarate, and aclidinium bromide/formoterol fumarate.

The use of LAMA/LABA combinations in the treatment of COPD has become increasingly widespread [8]. However, while dual therapy offers additive efficacy, it also entails potential safety risks. Currently, safety data for these agents are derived largely from clinical trials, which may not fully capture real-world safety profiles. Therefore, post-marketing safety evaluation of these products is warranted.

The Food and Drug Administration(FDA) Adverse Event Reporting System (FAERS) is one of the largest pharmacovigilance databases worldwide [9], and serves as an important tool for the FDA in post-marketing safety surveillance [10]. In this study, we conducted data mining on LAMA/LABA combinations using FAERS to evaluate their safety profiles and to provide evidence for clinical decision-making.

2 Materials and Methods

2.1 Data Source

FAERS data from the fourth quarter of 2013 through the fourth quarter of 2025 were included, covering patient demographics, drug information, and other relevant details.

2.2 Data Processing

After data cleaning, adverse event(AE) Reports with umeclidinium/vilanterol, indacaterol/glycopyrronium, tiotropium/olodaterol, glycopyrronium/formoterol, and aclidinium/formoterol as the primary suspect(PS) drugs were retrieved.

2.3 Data Analysis

Signal detection was performed using the Reporting Odds Ratio (ROR) and the Multi-Item Gamma Poisson Shrinker (MGPS) methods. The calculations were based on the four-fold contingency table for disproportionality analysis, as shown in Table 1. For the ROR method, the criteria for a positive signal were a report count of at least 3 and a lower bound of the 95% confidence interval for the ROR exceeding 1. For the MGPS method, the criterion was an the 95% credible lower limit of the empirical Bayes geometric mean (EBGM05) greater than 2 [11]. The analytical procedures are summarized in Table 2.

Table 1
Four-Cell Table of Proportional Imbalance Method

Project	Target AEs	Other AEs	Total
Target Drug	a	b	a + b
Other Drugs	c	d	c + d
Total	a + c	b + d	N = a + b + c+d

Table 2
Signal Detection Calculation Method

Method	Calculation Formula	Judgement criteria
ROR Method	ROR= $\frac{a/b}{c/d}$ 95%CI=$e^{\ln ROR \pm 1.96\sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}}$	95%CI > 1, a ≥ 3
MGPS Method	$EBGM = \frac{a(a+b+c+d)}{(a+c)(a+b)}$ $95\%\mathrm{CI} = e^{\ln(EBGM) \pm 1.96\sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}}$	EBGM05 > 2

2.4 Signal Classification

Signals were classified according to the System Organ Class (SOC) of the Medical Dictionary for Regulatory Activities (MedDRA).

3 Results

3.1 Basic Information

A total of 3,074 AE reports were identified for LAMA/LABA combinations, with umeclidinium/vilanterol accounting for the largest share (1,674), followed by indacaterol/glycopyrronium (674), tiotropium/olodaterol (572), glycopyrronium/formoterol (102), and aclidinium/formoterol (52). In terms of patient sex, females slightly outnumbered males for umeclidinium/vilanterol and glycopyrronium/formoterol, whereas the reverse was true for the other three agents. With regard to age, patients aged over 65 years constituted the majority for all five drugs. Regarding treatment duration, reports within 30 days were the most frequent for each agent. As for the reporting countries, the United States was the most common reporter for umeclidinium/vilanterol, tiotropium/olodaterol, and glycopyrronium/formoterol; Brazil for indacaterol/glycopyrronium; and the United Kingdom for aclidinium/formoterol. Detailed information is presented in Table 3.

Table 3
Basic Information of AE Reports

Characteristics		umeclidinium/vilanterol		indacaterol/glycopyrronium		tiotropium/olodaterol		glycopyrronium/formoterol		aclidinium/f	
			Reported Numb		Reported Numb		Reported Numb		Reported Numb		Repor Numb
Total		1674		674		572		102		52	
	Male		674		264		298		48		33
	Female		719		174		270		51		17
	Missing		281		236		4		3		2
Age/year	≤ 18		0		0		0		0		0
	19–45		9		1		3		1		0
	46–65		273		73		139		17		14
	> 65		677		175		347		60		30
	Missing		715		425		83		24		8
Duration of medication/d	≤ 30		219		87		74		19		13
	31–180		85		57		53		3		8
	181–365		54		24		38		1		2
	> 365		87		33		21		2		7
	Missing		1229		473		386		77		22
Occr_country		US	1154	BR	151	US	365	US	80	GB	9
		GB	108	DE	70	BR	33	DE	3	DE	7
		JP	57	HU	67	JP	22	JP	2	GR	4
		KR	44	IN	63	RU	17	EU	1	CA	3
		PL	43	MX	49	DE	14			US	2
										EU	2

3.2 SOC Distribution

The numbers of AE signals detected for umeclidinium/vilanterol, indacaterol/glycopyrronium, tiotropium/olodaterol, glycopyrronium/formoterol, and aclidinium/formoterol were 140, 111, 64, 30, and 10, respectively, corresponding to 19, 16, 15, 12, and 7 involved SOCs. The signals were predominantly mapped to SOCs such as cardiac disorders, infections and infestations, injury, poisoning and procedural complications, respiratory, thoracic and mediastinal disorders, and eye disorders. The distribution of signals and SOCs is illustrated in Fig. 1. Regarding cardiac disorders, the proportions of reports for the five drugs were 9.85%, 8.44%, 15.76%, 8.77%, and 5.56%, respectively; for infections and infestations, 13.74%, 9.56%, 12.32%, 10.09%, and 5.56%; for injury, poisoning and procedural complications, 5.06%, 7.26%, 2.44%, 21.05%, and 9.26%; and for respiratory, thoracic and mediastinal disorders, 36.26%, 48.23%, 44.27%, 26.75%, and 61.11%. The SOCs and their corresponding report proportions are shown in Fig. 2.

3.3 AE Signals

The top 30 AE signals for each of the five dual bronchodilators, ranked by report frequency, are presented in Supplementary Table 1. For umeclidinium/vilanterol, the more frequently reported signals included dyspnoea, pneumonia, cough, urinary retention, and myocardial infarction. For indacaterol/glycopyrronium, these included dyspnoea, cough, pneumonia, wheezing, and chest pain. For tiotropium/olodaterol, the signals comprised dyspnoea, pneumonia, cardiac failure, myocardial infarction, and respiratory failure. For glycopyrronium/formoterol, the list included dyspnoea, pneumonia, myocardial infarction, and atrial fibrillation. For aclidinium/formoterol, the signals included dyspnoea, cough, wheezing, swollen tongue, and palpitations.

4 Discussion

The most frequently reported AE signals for LAMA/LABA identified in this study included cough, dyspnoea, myocardial infarction, chest pain, and urinary retention, among others. These findings are largely consistent with existing clinical observations and product labelling. Drawing on relevant studies, we now discuss the safety profile of this drug class.

4.1 Respiratory, thoracic and mediastinal disorders

Within this SOC, the AE signals detected for all five drugs included dyspnoea and chronic obstructive pulmonary disease. For umeclidinium/vilanterol, the signals comprised 24 events: cough, lung disorder, choking, oropharyngeal pain, dysphonia, productive cough, wheezing, pneumothorax, pulmonary mass,

bronchospasm, emphysema, pulmonary congestion, pulmonary hypertension, bronchial obstruction, paradoxical bronchospasm, hypercapnia, pharyngeal oedema, choking sensation, dry throat, pulmonary thrombosis, intensive care, chronic bronchitis, sputum increased, and stridor. For indacaterol/glycopyrronium, there were 33 signals: cough, productive cough, lung disorder, wheezing, choking, dyspnoea exertional, dysphonia, emphysema, asphyxia, respiratory failure, sputum discoloured, throat irritation, asthmatic crisis, bronchiectasis, respiratory disorder, bronchospasm, pneumonitis, catarrh, dry throat, obstructive airways disorder, sleep apnoea syndrome, increased bronchial secretion, lung hyperinflation, nasal polyps, pulmonary mass, bronchitis chronic, respiratory arrest, choking sensation, apnoea, hypercapnia, pleural adhesion, pulmonary pain, and rales. For tiotropium/olodaterol, the signals were 15: respiratory failure, acute respiratory failure, dysphonia, pneumothorax, pleural effusion, pulmonary hypertension, pulmonary oedema, emphysema, hypoxia, choking, respiratory distress, asphyxia, asthmatic crisis, bronchospasm, and obstructive airways disorder. For glycopyrronium/formoterol, the signals included wheezing, productive cough, pneumothorax, and lung disorder. For aclidinium/formoterol, they were cough and wheezing. Among these, cough and dyspnoea were the most frequently reported.

Cough and bronchospasm are explicitly mentioned in the prescribing information for tiotropium/olodaterol. Rabe K F have suggested that dyspnoea and wheezing may be related to underlying undiagnosed cardiovascular conditions (e.g., heart failure, arrhythmia), airway hyperresponsiveness (e.g., comorbid asthma), pneumonia, pulmonary embolism, or allergy to drug excipients, rather than representing drug-induced paradoxical bronchoconstriction [4]. In our study, the respiratory system showed a relatively high number of AE signals for umeclidinium/vilanterol, indacaterol/glycopyrronium, and tiotropium/olodaterol, indicating the need for close monitoring of respiratory changes during treatment. Cough, the most common respiratory symptom, involves multiple mechanisms including airway mucosal irritation and increased cough reflex sensitivity [12]. Some studies have suggested that LABA agents may directly induce cough, with a higher incidence compared with LAMA monotherapy [2]. Furthermore, after oral inhalation, local adverse effects such as dysphagia-like symptoms may occur due to drug particle deposition in the oropharynx and direct irritation from propellants or excipients [13], and thorough mouth rinsing can significantly reduce their occurrence [14]. Regarding serious signals such as pulmonary congestion, pulmonary hypertension, and respiratory failure, although their report counts were relatively low, they often occurred in elderly patients with severely compromised baseline pulmonary function or coexisting systemic diseases [15]. Thus, the potential negative impact of these drugs on respiratory reserve deserves attention.

4.2 Cardiac disorders

Within this SOC, the signals detected for umeclidinium/vilanterol included 14 events: myocardial infarction, atrial fibrillation, cardiac failure, congestive cardiac failure, arrhythmia, angina pectoris, cardiac arrest, angina unstable, extrasystoles, stress cardiomyopathy, ventricular extrasystoles, cardiac discomfort, cardiac fibrillation, and hypertensive cardiomyopathy. For indacaterol/glycopyrronium, the signals comprised 12 events: cardiac failure, cardiopulmonary failure, cardiac disorder, cardiac arrest, arrhythmia, cardio-respiratory arrest, angina pectoris, cardiovascular disorder, myocardial ischaemia, angina unstable, cardiomegaly, and coronary artery stenosis. For tiotropium/olodaterol, there were 11 signals: cardiac failure, myocardial infarction, cardiac arrest, cardiac disorder, cardiac failure congestive, coronary artery disease, cardio-respiratory arrest, myocardial ischaemia, cardiac failure chronic, left ventricular failure, and ventricular extrasystoles. For glycopyrronium/formoterol, the signals were myocardial infarction and atrial fibrillation; for aclidinium/formoterol, palpitations. Among these, myocardial infarction and cardiac failure were among the more frequently reported. The prescribing information for glycopyrronium/formoterol, umeclidinium/vilanterol, tiotropium/olodaterol, and indacaterol/glycopyrronium all mention cardiac events such as atrial fibrillation, palpitations, supraventricular tachycardia, and tachycardia. Real-world data have shown that among COPD patients without baseline cardiovascular disease, the 3-year cumulative incidence of cardiovascular events in the LAMA monotherapy group was as high as 0.202, with a particularly prominent risk of atrial fibrillation, suggesting that LAMA alone may confer a higher risk of new-onset atrial fibrillation compared with LABA [16]. Long-term use of LABA agents may, through β_2-receptor agonism, concurrently activate cardiac β_1-receptors, leading to increased heart rate and myocardial oxygen consumption, thereby inducing or exacerbating underlying arrhythmias and ischaemic events [17]. In contrast, LAMA agents primarily act on airway M_3 receptors, although they may also block cardiac M_2 receptors [18]. Nevertheless, a large-scale clinical trial showed no significant difference in cardiovascular safety endpoints compared with placebo [19]. In our study, the report counts for unstable angina, palpitations, and angina pectoris were also relatively high, suggesting that routine monitoring of electrocardiograms and cardiac biomarkers during treatment is advisable, particularly in patients with hypertension, diabetes mellitus, or a history of cardiovascular events. Of note, although the numbers of reports for myocardial infarction and cardiac arrest were relatively low, these events carry a very poor prognosis and are therefore of major clinical concern [20]. Furthermore, as highlighted by Matera et al. [21], although the overall risk of cardiovascular AE reports with LAMA appears to be reduced in combination therapy, there are differences among individual LAMA agents, and the cardiovascular risk signals of newer LAMA agents warrant closer attention.

4.3 Infections and infestations

In the SOC of infections and infestations, the signals detected for umeclidinium/vilanterol comprised 12 events: pneumonia, bronchitis, lower respiratory tract infection, lung infection, candida infection, staphylococcal infection, eye infection, lung abscess, liver abscess, nosocomial infection, pulmonary mycosis, and tinea infection. For indacaterol/glycopyrronium, the signals included 12 events: pneumonia, bronchitis, pseudomonas infection, lung infection, respiratory tract infection, achromobacter infection, skin bacterial infection, pseudomonas bronchitis, tuberculosis, hordeolum, infective exacerbation of chronic obstructive airways disease, and viral upper respiratory tract infection. For tiotropium/olodaterol, the signals were pneumonia, bronchitis, infective exacerbation of chronic obstructive airways disease, and pneumonia bacterial. For glycopyrronium/formoterol, the signals comprised pneumonia and bronchitis; for aclidinium/formoterol, only respiratory tract infection was identified. Among these, pneumonia and bronchitis were the most frequently reported. Except for aclidinium/formoterol, pneumonia was detected in all five drugs. Tiotropium/olodaterol and indacaterol/glycopyrronium yielded relatively more infection-related signals, suggesting that vigilance during treatment is warranted. The prescribing information and long-term safety trials have indicated that the most common serious adverse events(SAEs) for tiotropium/olodaterol were COPD exacerbation and pneumonia; aclidinium/formoterol, umeclidinium/vilanterol, and tiotropium/olodaterol have also reported infectious events such as sinusitis and urinary tract infection, suggesting that these agents are not limited to respiratory tract infections but may also pose risks at other sites. LAMA/LABA combinations improve ventilation through bronchodilation [22], and while they may reduce mucus secretion and enhance mucociliary clearance [23], acute exacerbations of COPD still occur, so close attention to this adverse event remains essential. A network meta-analysis indicated that LAMA or LABA alone or in combination did not significantly

increase the risk of pneumonia compared with placebo [24]. Should such AEs occur, close monitoring for signs of infection and timely anti-infective therapy are recommended during treatment.

4.4 General disorders and administration site conditions

Within this SOC, the signals identified for umeclidinium/vilanterol included chest discomfort, ill-defined disorder, apparent death, and nonspecific reaction. For indacaterol/glycopyrronium, the signals comprised malaise, chest pain, chest discomfort, concomitant disease aggravated, secretion discharge, sensitivity to weather change, apparent death, polyp, general physical condition abnormal, and sensation of foreign body. For glycopyrronium/formoterol, only chest discomfort was detected; no signals were found for tiotropium/olodaterol or aclidinium/formoterol.

The signal of apparent death is an extremely rare but serious event, characterized by profound depression of consciousness and reflexes, which can be easily misdiagnosed as clinical death [25]. Although this signal was detected in our mining, it is not currently documented in the prescribing information for these agents. This finding suggests that when clinicians encounter patients with deep disturbances of consciousness and undetectable spontaneous respiration or circulation, they should employ electrocardiographic and other relevant examinations to comprehensively assess residual vital functions, so as to avoid premature determination of irreversible death [25]. In addition, caution should be exercised regarding potential reporting bias or confusion with other serious events such as respiratory failure. Chest pain is described in the prescribing information for glycopyrronium/formoterol, umeclidinium/vilanterol, and indacaterol/glycopyrronium. Although not explicitly listed for aclidinium/formoterol, chest pain is mentioned in the overdose section as a possible symptom of excessive use. Chest pain and chest discomfort should be differentiated from cardiac events and respiratory muscle fatigue; in some patients, severe coughing or bronchospasm may lead to secondary chest wall muscle strain, presenting as non-cardiac chest pain [26].

4.5 Eye disorders

Within this SOC, the signals detected for umeclidinium/vilanterol included visual impairment, glaucoma, blindness, macular degeneration, ocular discomfort, photopsia, angle closure glaucoma, and blindness transient. For indacaterol/glycopyrronium, the signals comprised glaucoma, blindness unilateral, ocular hypertension, and orbital oedema. For tiotropium/olodaterol, they included macular degeneration and photopsia. For glycopyrronium/formoterol, the signals were cataract, eye disorder, and glaucoma. No signals were identified for aclidinium/formoterol. The prescribing information for umeclidinium/vilanterol mentions conjunctivitis, while that for tiotropium/olodaterol explicitly lists glaucoma, increased intraocular pressure, and blurred vision. As LAMA/LABA combinations contain an anticholinergic component, they may induce or aggravate angle-closure glaucoma through systemic absorption or local mydriatic effects, and may also affect aqueous humour circulation [27]. For patients with a history of angle-closure glaucoma, it is advisable to inform the ophthalmologist before initiation of therapy. Should symptoms such as blurred vision, eye pain, or halos appear after use, immediate medical attention is warranted [28]. None of the product labels for the above drugs list cataracts as a common or definite adverse reaction. Therefore, visual impairment and cataracts may not be typical ADRs for this drug class; they could be related to drug-induced ciliary muscle accommodation paralysis or changes in lens osmotic pressure [29].

4.6 Gastrointestinal disorders

Within this SOC, the signals detected for umeclidinium/vilanterol included swollen tongue, lip swelling, retching, mouth swelling, intestinal haemorrhage, and gingival pain. For indacaterol/glycopyrronium, they comprised dry mouth, aphthous ulcer, abnormal faeces, ileus, and loose tooth. For tiotropium/olodaterol, the signals were gastritis and ileus. For aclidinium/formoterol, only swollen tongue was identified; no signals were found for glycopyrronium/formoterol. Dry mouth is mentioned in nearly all LAMA/LABA prescribing information, with an incidence ranging from 1% to 3% or higher. This effect results from inhibition of salivary gland secretion by the anticholinergic component. Although not life-threatening, it can substantially affect patients' quality of life and medication adherence. Intestinal obstruction, including paralytic ileus, is explicitly documented in the prescribing information for tiotropium/olodaterol and is classified as a rare but SAE. Patients with COPD often have chronic constipation, and in such individuals, there is a very low probability of precipitating paralytic ileus, particularly in the elderly or those who are bedridden [30]. Tongue swelling may be related to allergic reactions; although rare, it can progress to airway obstruction [31]. The prescribing information advises that patients with known allergy to any component should not use these agents, and that immediate discontinuation is warranted if tongue swelling or difficulty swallowing occurs. Mouth swelling may be associated with increased oropharyngeal drug deposition from inhaled powder formulations; thorough mouth rinsing after use can alleviate such discomfort. In addition, soft-mist inhalers, which produce slower aerosol particles and result in less oropharyngeal deposition, may also help reduce these local effects [14].

4.7 Investigations

Within this SOC, the signals detected for umeclidinium/vilanterol included heart rate increased, oxygen saturation decreased, bronchoscopy, carbon dioxide increased, colonoscopy, and protein urine present. For indacaterol/glycopyrronium, the signals comprised blood pressure systolic increased, body height decreased, body temperature decreased, forced expiratory volume decreased, glomerular filtration rate decreased, neutrophil count increased, pulmonary function test decreased, body surface area decreased, and urine output decreased. For tiotropium/olodaterol, the signals were oxygen saturation decreased, heart rate irregular, and blood magnesium decreased. For glycopyrronium/formoterol, they included oxygen saturation decreased and body height decreased. No signals were identified for aclidinium/formoterol. The prescribing information for glycopyrronium/formoterol, tiotropium/olodaterol, and indacaterol/glycopyrronium mentions tachycardia and palpitations; tiotropium/olodaterol also lists cardiac arrhythmias (atrial fibrillation, supraventricular tachycardia). The LABA component of LAMA/LABA combinations may increase heart rate through activation of cardiac β_1 receptors [32], and the associated hypokalaemia can prolong the QT interval, thereby increasing the risk of atrial and ventricular arrhythmias [33]. Meanwhile, the anticholinergic effect of LAMA may contribute to relative sympathetic overactivity, further exacerbating the increase in heart rate, Close monitoring through electrocardiography and serum potassium measurement is recommended, with the potential addition of cardioselective beta-blockers when necessary [34]. For high-risk patients with known cardiovascular disease or corrected QT interval(QTc) prolongation, regular electrocardiogram and potassium monitoring before and after treatment initiation is advisable. Under careful risk-benefit assessment, collaborative management with cardiology specialists may be considered when indicated [34]. Particular caution should be exercised in patients concurrently using other medications that may prolong the QTc interval (e.g., certain antiarrhythmic agents,

macrolide antibiotics, and antipsychotics), as the combination with LABA/LAMA may further elevate the risk of arrhythmias and warrants enhanced surveillance [35].

4.8 Injury, poisoning and procedural complications

Within this SOC, after excluding signals related to medication errors, the events identified for umeclidinium/vilanterol included hip fracture, head injury, spinal fracture, optic nerve injury, pelvic fracture, foreign body in respiratory tract, foreign body in throat, respiratory fume inhalation disorder. For indacaterol/glycopyrronium, the signals were foreign body aspiration and lumbar vertebral fracture. For tiotropium/olodaterol, they included hip fracture and pelvic fracture. No signals were detected for glycopyrronium/formoterol or aclidinium/formoterol. In the prescribing information for glycopyrronium/formoterol, falls are explicitly listed among adverse reactions with an incidence of 1% to 2%. Fracture and fall occurrence may be linked to drug-induced dizziness, muscle cramps, or potential effects on autonomic regulation that could predispose to orthostatic hypotension [36], compounded by polypharmacy, underlying comorbidities, and reduced mobility commonly seen in elderly patients [4]. Moreover, patients with COPD already have a higher baseline fall risk than the general population due to diminished exercise tolerance and muscle wasting [4]. It is therefore advisable to perform fall risk assessments in elderly or physically impaired patients and to consider treatment adjustments when necessary.

4.9 Other signals

In addition, other adverse event signals identified in this study for umeclidinium/vilanterol included urinary retention, malignant lung neoplasm, cerebrovascular accident, and dysuria, among others; for indacaterol/glycopyrronium, they included diabetes mellitus and lung neoplasm malignant; for tiotropium/olodaterol, lung neoplasm malignant and prostate cancer; for glycopyrronium/formoterol, memory impairment and lung neoplasm malignant; and for aclidinium/formoterol, rash pruritic and speech disorder. All of these signals ranked among the top 30 in terms of report counts for the respective drugs. Urinary retention is documented in the prescribing information for both tiotropium/olodaterol and indacaterol/glycopyrronium, and is attributed to the anticholinergic component's inhibition of detrusor contraction, particularly in patients with benign prostatic hyperplasia or elderly males [37]. Mechanistically, LAMA agents exhibit receptor-selectivity differences in their anticholinergic effects; although the M_3 receptor is targeted in the lung, systemic exposure may still affect bladder function, explaining the class-effect nature of urinary retention [38]. Prior to treatment, voiding function should be evaluated, and patients should be instructed to discontinue the drug and seek medical attention if dysuria occurs. Malignant lung neoplasm is not listed as a common adverse event in current product labels. Given that COPD patients often have a history of smoking, systemic inflammation, and cardiovascular risk factors, cerebrovascular accident and lung cancer may be more closely associated with underlying comorbidities and lifestyle factors than directly caused by the drug [4]. Speech disorder may be related to involuntary abnormal movements, impaired respiratory-phonatory coordination, or oromandibular muscle tone abnormalities [39]; however, the current prescribing information lacks explicit documentation of this event, and further data collection is needed to clarify the causal relationship. Clinicians should remain vigilant for these emerging signals during treatment, especially in patients with multiple risk factors.

5 Conclusion

This study detected and analyzed AE signals for dual bronchodilators using the ROR and MGPS methods based on the FAERS database, and provided a detailed discussion of their safety along with available data. The signals for all five drugs were predominantly concentrated in the SOCs of respiratory, thoracic and mediastinal disorders, cardiac disorders, and infections and infestations. Cough, dyspnoea, myocardial infarction, cardiac failure, and pneumonia were among the most frequently reported signals for most of the drugs, while novel signals such as fracture, apparent death, and malignant lung neoplasm were detected for some of them. During treatment, it is advisable to enhance monitoring of cardiopulmonary function and signs of infection, particularly in elderly patients and those with poor baseline cardiopulmonary status, so as to prevent serious adverse drug reactions(ADRs).

Abbreviations

COPD
Chronic Obstructive Pulmonary Disease
LABA
long-acting β_2-agonist
LAMA
long-acting muscarinic antagonist
GOLD
Global Initiative for Chronic Obstructive Lung Disease
ICS
inhaled corticosteroid
FDA
Food and Drug Administration
FAERS
The FDA Adverse Event Reporting System
PS
primary suspect
AE
adverse event
ROR
Reporting Odds Ratio

MGPS
Multi-Item Gamma Poisson Shrinke
EBGM05
the 95% credible lower limit of the empirical Bayes geometric mean
SOC
System Organ Class
MedDRA
Medical Dictionary for Regulatory Activities
SAE
serious adverse event
QTc
corrected QT interval
ADR
adverse drug reaction

Declarations

Data availability statement

Data presented in the current study can be found in the article or Supplementary Material, and for further inquiries please contact the corresponding authors.

Author contributions

Concept and design of the study: YP, YZ. Acquisition, analysis, and interpretation of data: WJC, TQX, JX. Drafting the manuscript: JXA,YP. All authors reviewed and approved the manuscript.

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Conflict of interest

The authors declare that there was no conflicts of interest disclosed.

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Figures

Fig1

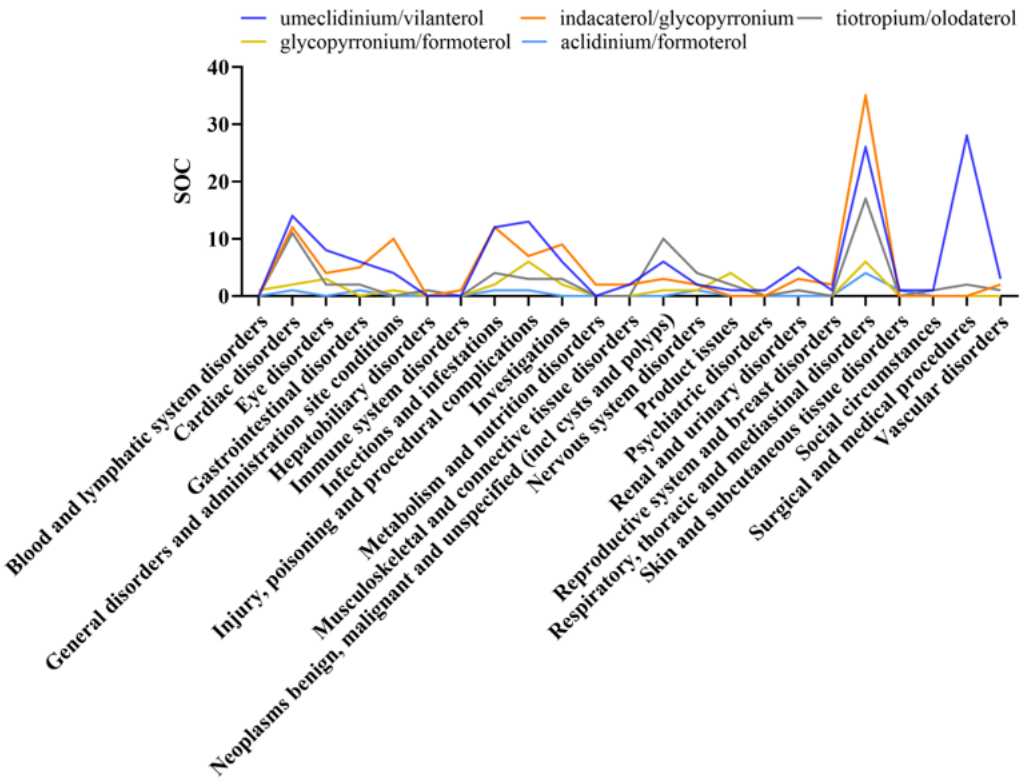


Figure 1

Distribution of AE signals and involved System Organ Classes (SOCs) for the five LAMA/LABA dual bronchodilators. The bar chart displays the total number of AE signals (blue bars) and the number of SOCs involved (orange bars) for each of the five drugs: umeclidinium/vilanterol (n = 1,674 reports), indacaterol/glycopyrronium (n = 674), tiotropium/olodaterol (n = 572), glycopyrronium/formoterol (n = 102), and aclidinium/formoterol (n = 52). Abbreviations: AE, adverse event; SOC, System Organ Class.

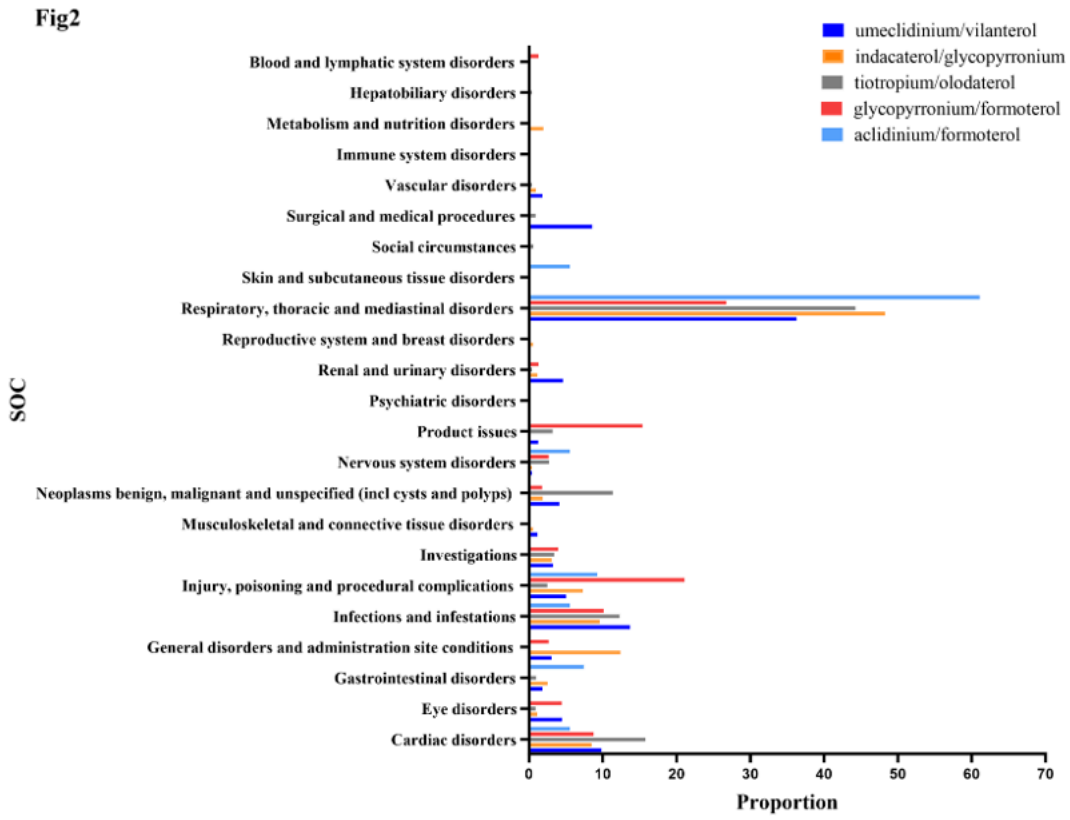


Figure 2

Proportion of AE reports mapped to the four major System Organ Classes (SOCs) for each of the five LAMA/LABA dual bronchodilators. The four SOCs presented are: respiratory, thoracic and mediastinal disorders (blue bars), cardiac disorders (orange bars), infections and infestations (green bars), and injury, poisoning and procedural complications (purple bars). Proportions are expressed as percentages of total AE reports for each drug. Abbreviation: AE, adverse event; SOC, System Organ Class.

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