pharmacoepidemiology

MDPI

Article

Suspected Adverse Drug Reactions Associated with Leukotriene Receptor Antagonists Versus First-Line Asthma Medications: A National Registry–Pharmacology Approach

Mohammed Khan, Christine Hirsch * and Alan M. Jones *

School of Pharmacy, University of Birmingham, Edgbaston B15 2TT, UK
* Correspondence: c.a.hirsch@bham.ac.uk (C.H.); a.m.jones.2@bham.ac.uk (A.M.J.)

Abstract

Background/Objectives: The aim of this study was to determine the suspected adverse drug reaction (ADR) profile of leukotriene receptor antagonists (LTRAs; montelukast and zafirlukast) relative to first-line asthma medications such as short-acting beta agonists (SABAs; salbutamol) and inhaled corticosteroid (ICS; beclomethasone) in the United Kingdom. to determine the chemical and pharmacological rationale for the suspected ADR signals. **Methods**: Properties of the asthma medications (pharmacokinetics and pharmacology) were datamined from the chemical database of bioactive molecules with drug-like properties, the European Molecular Biology Laboratory (ChEMBL). Suspected ADR profiles of the asthma medications were curated from the Medicines and Healthcare products Regulatory Authority (MHRA) Yellow Card interactive Drug Analysis Profiles (iDAP) and concatenated to the standardised prescribing levels (using Open Prescribing data) between 2018 and 2023. **Results**: Total ADRs per 100,000 R_x ($p < 0.001$) and psychiatric system organ class (SOC) ADRs ($p < 0.001$) reached statistical significance. Montelukast exhibited the greatest ADR rate at 15.64 per 100,000 R_x. **Conclusions**: Relative to the controls, montelukast displays a range of suspected system organ class level ADRs. For the credible and previously reported psychiatric ADRs, montelukast is statistically significant ($p < 0.001$). A mechanistic hypothesis is proposed based on polypharmacological interactions in combination with cerebrospinal fluid (CSF) levels attained. Montelukast had the highest nervous disorder ADR rate at 1.71 per 100,000 R_x, whereas beclomethasone and salbutamol had lower rates (0.43 and 0.14, respectively). These ADRs share a similar background to psychiatric ADRs with CSF penetrability involved and affecting the dopamine axis. This work further supports the monitoring of montelukast for rare but important neuropsychiatric side effects.

Keywords: montelukast; salbutamol; beclomethasone; zafirlukast; asthma; neuropsychiatric; adverse drug reactions; Yellow Card; pharmacology

check for updates

Academic Editor: Tanja Mueller

Received: 7 August 2025
Revised: 11 September 2025
Accepted: 11 September 2025
Published: 19 September 2025

Citation: Khan, M.; Hirsch, C.; Jones, A.M. Suspected Adverse Drug Reactions Associated with Leukotriene Receptor Antagonists Versus First-Line Asthma Medications: A National Registry–Pharmacology Approach. *Pharmacoepidemiology* **2025**, *4*, 18. https://doi.org/10.3390/pharma4030018

Correction Statement: This article has been republished with a minor change. The change does not affect the scientific content of the article and further details are available within the backmatter of the website version of this article.

Copyright: © 2025 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

1. Introduction

Asthma is a common respiratory condition worldwide. In the UK, 5.4 million people receive treatment, which equates to approximately 1 in 12 adults and 1 in 11 children [1]. This condition is responsible for approximately 3% of primary consultations, 200,000 bed days, and 60,000 hospital admissions per year in the UK [2]. Asthma can affect people of all ages and can range in severity from very mild, infrequent wheezing to severe life-threatening closure of the airways [3]. The economic cost of asthma in the UK is greater

than GBP 1bn per annum. which includes medication costs, healthcare professionals' time, diagnostic tests, and secondary care treatment [4]. The treatment of asthma involves a stepwise approach, depending on the severity and level interventions required to manage symptoms [5]. Short-acting beta agonists (SABAs), for example, salbutamol, is a 'reliever' therapy and the first-line treatment in the UK prior to updated NICE guidance in November 2024 [6]. If asthma is uncontrolled with a SABA, an inhaled corticosteroid (ICS), for example, beclomethasone, is prescribed as a maintenance therapy. Should symptoms persist, 'add-ons' can be given, for example, leukotriene receptor antagonists (LTRAs). In the UK, montelukast and zafirlukast are licensed LRTAs (zafirlukast was discontinued in the UK on 31 March 2018) (Figure 1). These drugs prevent the pro-inflammatory effects of cysteinyl leukotrienes (*CysLT1*) at their receptors found on the smooth muscles of bronchioles, which helps reduce the levels of inflammation and sensitivity of the airways to asthma triggers [7].

All drugs can result in adverse drug reactions (ADRs) and can be classified by the DoTS system (dose of the drug, time course of the reaction, and susceptibility factors) [8]. Table 1 highlights the common adverse effects reported with asthma medications prior to this study. It should be noted that ICSs are usually combined with SABAs; thus, the side effects in Table 1 may not be correlated to ICS alone [9].

Table 1. Common side effects of asthma medications [9].

Short-Acting Beta-2 Agonist	Inhaled Corticosteroid	Leukotriene Receptor Antagonist
Arrythmias	Arrythmias	Aggressive behaviour
Fine tremor	Fine tremor	Anxiety
Headache	Headache	Headache
Tachycardia	Tachycardia	Hallucinations
		Sleeping issues
		Abdominal pain

An extensive cohort study of electronic health records (EHRs) found that montelukast was associated with higher odds of neuropsychiatric outcomes [10]. Studies have highlighted an increased risk of neuropsychiatric side effects in paediatric and adolescent patients prescribed montelukast [11], but conflicting findings have found no association in this age group [12]. Nightmares have also been associated with montelukast use, especially in children, that generally disappear upon discontinuation [13]. Lee et al. noted the rare occurrence of Churg–Strauss syndrome and a lack of sufficient data on neuropsychiatric effects such as anxiety, depression, sleep disturbance, and suicidality with montelukast use in South Korea [14].

An exploration of neuropsychiatric adverse events associated with montelukast in the FAERS database demonstrated risks of suicide ideation and depression. In turn, several genes associated with mood and depressive disorders were enriched, warranting future research on any pharmacological mechanisms at play [15]. Intriguingly, a systematic review found no significant association between montelukast and suicide-related events or depression. However, patients concomitantly taking antidepressants identified significant associations for these side effects, casting doubt on montelukast's role [16].

However, the UK regulator (MHRA) has strengthened side effect warnings for behavioural and neuropsychiatric side effects associated with montelukast [17].

During the writing of this paper, Yao et al. reported a comparative risk of neuropsychiatric adverse events with LRTAs vs. ICSs [18]. A 6–88% heightened risk of neuropsychiatric adverse events with montelukast vs. ICS was detected.

Given the conflicting findings regarding the association of neuropsychiatric side effects with the LRTAs reported in previous studies, a pharmacoepidemiology study is necessary to explore the differential ADRs between LRTAs vs. SABAs vs. ICSs and to identify

any pharmacological mechanisms in operation that influence the ADR profile of these representative drugs [19–24].

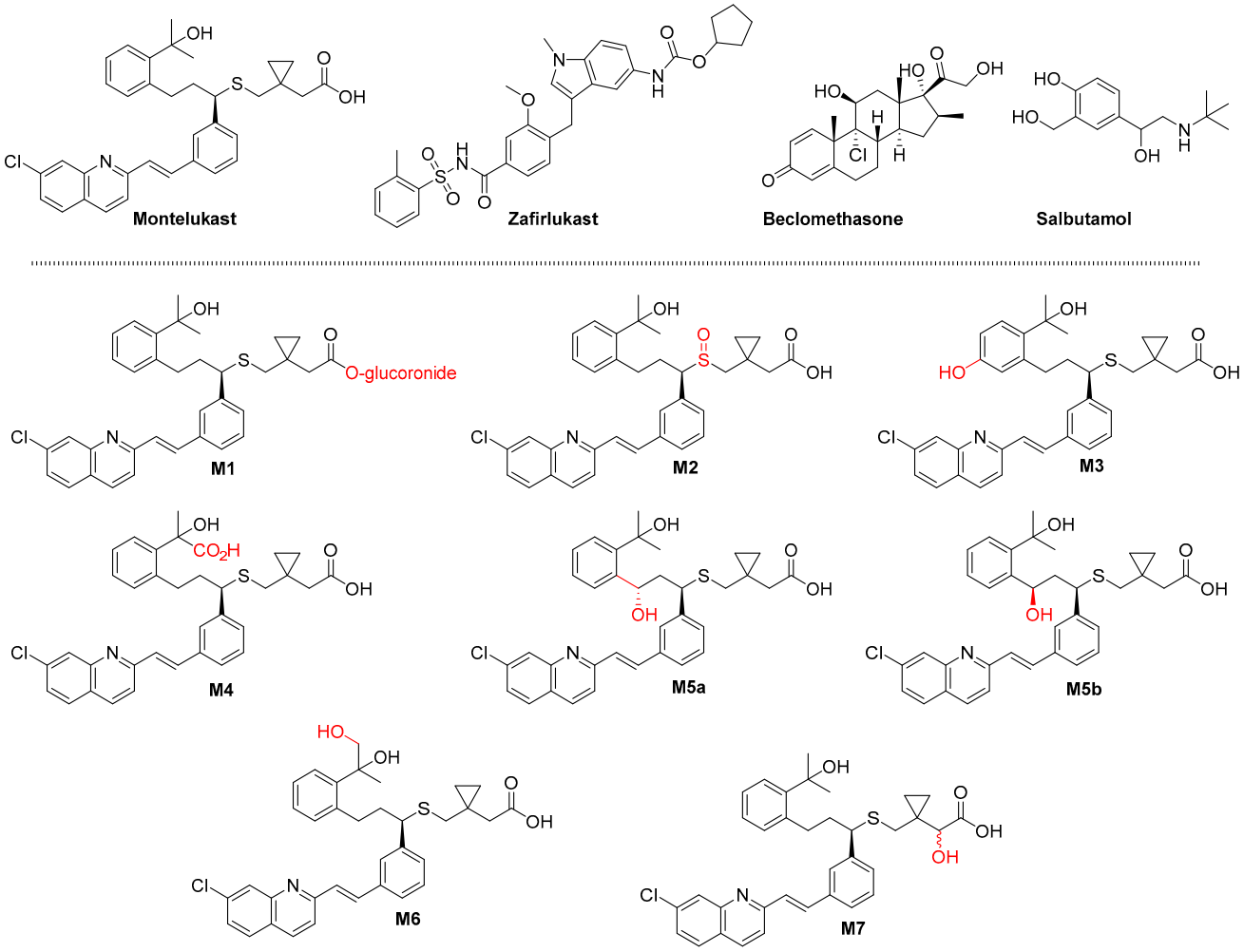


Figure 1. Structures of asthma medications studied (LRTAs: montelukast and zafirlukast; controls: ICS, beclomethasone and SABA, salbutamol) and the reported circulating metabolites of montelukast: M6 is the major primary metabolite formed and M4 is a secondary metabolite found in bile, with other metabolites in much lower concentrations [25–27]. Groups coloured in red are the metabolic changes to montelukast.

Herein, we investigate LRTAs for suspected ADR signals reported between 2018 and 2023 with salbutamol and beclomethasone as the most prescribed first-line SABAs and ICS (maintenance preventor therapy comparators) and explore the unique polypharmacology of the drugs' for associations with statistically significant suspected ADRs.

This is a novel approach in pharmacoepidemiology, and asthma more specifically, wherein the combination of national pharmacovigilance data with the chemical and pharmacological profiles of asthma treatments are analysed together to explore mechanistic rationales for ADR signals.

2. Results

2.1. Molecular Properties

The structures of the medications studied are shown in Figure 1. The following information was extracted from the databases: EMC—dosage and clinical indications for the target drug(s); ChEMBL—target bioactivity IC_{50} values for the target drug(s);

DrugBank—PK parameters; and PubChem—physical properties and structure descriptors of the target drug(s).

The prediction of BBB penetration was determined by whether the physiochemical properties of the drugs meet requirements and thresholds to allow for penetration. The specific requirements were as follows: molecular weight < 450 Da, ^{t}PSA < 90 Å, neutral or basic characteristics based on p*K*a, <6 hydrogen bond donors and <2 hydrogen bond acceptors, a clog$D_{7.4}$ between 1 and 3, and not a P-glycoprotein (P-gp) substrate. P-gp is an efflux transporter located in the BBB that expels drugs and other molecules from the brain into the bloodstream. The greater number of requirements met, the higher the predicted BBB penetration risk [28]. The physicochemical properties of montelukast, zafirlukast and the controls, beclomethasone and salbutamol, are displayed in Table 2.

Table 2. Physiochemical and BBB properties of montelukast, zafirlukast, beclomethasone, and salbutamol.

Variables	Montelukast	Zafirlukast	Beclomethasone	Salbutamol
pIC_{50}	8.64	8.74	8.08	6.01
$clog_{10}P$	8.49	6.4	2.15	0.34
LLE	0.15	2.34	5.93	5.67
MW (Da)	586.2	575.69	408.92	239.31
pK_a	4.4 (acidic)	4.29 (acidic)	12.44 (neutral)	9.4 (basic)
^{t}PSA (Å)	70.42	115.73	94.83	72.72
HB acceptors	4	7	5	4
HB donors	2	2	3	4
$clog_{10}D_{7.4}$	5.8	5.46	2.15	−1.32
P-glycoprotein Substrate	Yes	Yes	Yes	Yes
No. of BBB requirements met	2	1	4	4

Montelukast was the most lipophilic drug ($clog_{10}P$ = 8.49) and zafirlukast was the most potent (pIC_{50} = 8.74). Montelukast and zafirlukast both had an LLE significantly <5 (0.15 and 2.34, respectively). Salbutamol and beclomethasone met both the molecular weight requirement (<450 Da) and were either neutral or basic. Montelukast and salbutamol had a ^{t}PSA < 90 Å (70.42 Å and 72.72 Å, respectively). No drugs had less than two hydrogen bond acceptors; however, all drugs had less than six hydrogen bond donors. Only beclomethasone had a clog$D_{7.4}$ between 1 and 3 (2.15). All selected drugs are P-glycoprotein substrates, but the P-gp efflux mechanism declines with age.

2.2. Pharmacokinetic Properties

The pharmacokinetic properties included bioavailability (%*F*), half-life ($t_{1/2}$), T_{max} (time to reach the max concentration), C_{max} (peak plasma concentration), whether it was metabolised by a CYP P_{450} enzyme isoform, renal clearance (Cl), volume of distribution (V_d), total clearance (L), and plasma protein binding (PPB). C_{max} was converted from ng/mL to nM. The pharmacokinetic properties of the LTRAs and the controls are shown Table 3. Zafirlukast had the highest bioavailability of *F* = 100% (oral), while the lowest was salbutamol at 24.8%. The T_{max} was the same for montelukast and zafirlukast (3 h) but lower for beclomethasone and salbutamol (0.7 h and 0.17 h, respectively). All drugs were metabolised by cytochrome P_{450} (CYP) familial isoforms. The V_d of salbutamol was highest (143.2 L) and the lowest was montelukast (8–11 L). Montelukast and zafirlukast had high plasma protein binding (PPB) of 99% compared to that of salbutamol at 10%.

Table 3. Pharmacokinetic properties of montelukast, zafirlukast, beclomethasone, and salbutamol.

Variables	Montelukast	Zafirlukast	Beclomethasone	Salbutamol
Bioavailability (%F)	64%	100%	41%	24.8%
Half-life (h)	2.7–5.5	8–16	5.7	2.7–5.5
Tmax (h)	3	3	0.7	0.17
Cmax (nM)	656.77	442.95	86.46	1678.83
CYP metabolism	CYP3A4, CYP28C, CYP28B	CYP2C9	CYP430 3A	CYP 450
Renal excretion	<0.2%	10%	negligible	272 ± 38 mL/min
Volume of distribution (L)	8–11	70	20	156 ± 38 (IV)
Clearance (L/h)	2.7	20	150	25.22
PPB (%)	99%	99%	87%	10%

2.3. Pharmacology Properties

The pharmacology results show the clinically significant values in green with an inhibitory value below the C_{max} threshold (Table 4). A threshold was created (×1.5) to include off-target pharmacological activities that may fall outside the C_{max} due to differential dosing regimens. Montelukast was the most potent towards its target receptor, cysteinyl leukotriene receptor 1 (2.3 nM), followed by zafirlukast (8.7 nM). Montelukast showed potent interaction with the off-target, adenosine A3 receptor (43 nM). Both montelukast and zafirlukast were potent towards the off-target, MAP kinase p38 alpha (856 nM and 6.5 nM, respectively). Zafirlukast interacted with the off-target, MAP kinase ERK2 (538 nM). Salbutamol was potent towards its on-target protein beta-2 adrenergic receptor (980 nM). Beclomethasone was potent towards its on-target receptor, glucocorticoid receptor (8.2 nM). Montelukast and zafirlukast were found to have potent interactions with additional off-target proteins (Table 3).

Table 4. Pharmacology properties of montelukast, zafirlukast, beclomethasone and salbutamol (nM).

Protein Group	Protein Compound	Montelukast	Zafirlukast	Beclomethasone	Salbutamol
G Protein coupled receptors	Cysteinyl leukotriene receptor 1	2.3	8.7		
	Cysteinyl leukotriene receptor 2	27,000	7397		
	Alpha-2a adrenergic receptor	3919			
	Alpha-2c adrenergic receptor	5279			
	Adenosine A1 receptor		>10,000		
	Adenosine A3 receptor	434	1363		
	Beta-2 adrenergic receptor	3488			980
	Beta-3 adrenergic receptor	4300			
	Dopamine D1 receptor		>10,000		
	Dopamine D3 receptor	7747			
	Delta opioid receptor	4795			
	Mu opioid receptor		>10,000		
	Norepinephrine receptor	2689			
	Histamine H1 receptor		>10,000		
	Neurokinin 2 receptor	3822			
	Muscarinic acetylcholine receptor M1	8045			
	Muscarinic acetylcholine receptor M3	6626			
	Serotonin 2b (5T-HT2b) receptor	6256			

Table 4. *Cont.*

Protein Group	Protein Compound	Montelukast	Zafirlukast	Beclomethasone	Salbutamol
Transmembrane protein	Dopamine transporter	2601			
	Epidermal growth factor 1 erbB1	3197	5751		
MAPEG	Leukotriene C4 synthase	<5000			
	Prostaglandin E synthase		18,100		
MAP	MAP kinase p38 alpha	856	6.4		
	MAP kinase ERK1		4376		
	MAP kinase ERK2		538		
CYP5	Thromboxane A synthase	1525	3810		
Src family kinases (SFKs)	Tyrosine-protein kinase FYN	4702			
CYP 450	Cytochrome P450 2C8	1000			
SLC10 family of solute carrier proteins	Bile acid transporter		6500		
ABC superfamily transport proteins	Bile salt export pump		11,100	16,985	>1,000,000
APC transport family	Multidrug resistance-associated protein 1		1300		
	Multidrug resistance-associated protein 2		7600		
	Multidrug resistance-associated protein 4		12,100		>133,000
	Canalicular multispecific organic anion transporter 1		58,800		>133,000
	Canalicular multispecific organic anion transporter 2		>133,000		>133,000
Group IVA cytosolic	Cytosolic phospholipase A2		85,000		
Nuclear receptor family	Glucocorticoid receptor			8.2	
Protein superfamily	Thiosulfate sulfur transferase				>100,000
Other	Epoxidase hydratase		2000		
C max (nM)		657	443	86	1679
Threshold (×1.5)		985	664	130	2518
Legend	blank = unknown	Green = Clinically significant			

2.4. ADRs

Total ADRs and psychiatric ADRs were found to be statistically significant at the SOC level (Table 5). Further exploration of psychiatric ADRs at HLGT level is shown in Table 6. Montelukast provided a much higher ADR rate per 100,000 R_x in multiple organ class categories including cardiac disorder 0.13 (compared to 0.1 and 0.06 beclomethasone and salbutamol, respectively), gastrointestinal disorder (1.08), nervous system disorders (1.71), and psychiatric disorders (8.22) per 100,000 R_x. Montelukast was the only drug with a completed suicide ADR rate at 0.01 per 100,000 R_x (n = 3 subjects), whereas the others showed a value of zero. Table 4 also shows that montelukast had a higher respiratory, thoracic, and mediastinal disorders than both beclomethasone and salbutamol but did not reach significance.

Table 5. Summary of suspected ADR profiles of montelukast, zafirlukast, beclomethasone and salbutamol in the UK (the number in parentheses represents the standardisation to 100,000 R_x). *p*-values were calculated using a chi-squared test. Supporting data can be found in Table S1.

Variables	Montelukast	Zafirlukast	Beclomethasone	Salbutamol	*p*
Total prescriptions	18,757,214	1327	70,250,968	107,619,145	-
Total ADRs	2935 (15.64)	9 (678.22)	2327 (3.37)	1342 (1.24)	<0.001
Fatalities	2 (0.01)	0 (0)	1 (0)	15 (0.01)	0.95
Cardiac disorder	26 (0.13)	0 (0)	71 (0.1)	68 (0.06)	0.98
Fatalities	0 (0)	0 (0)	0 (0)	0 (0)	-
Palpitations	23 (0.12)	0 (0)	59 (0.08)	24 (0.02)	0.96
Gastrointestinal disorder	204 (1.08)	0 (0)	221 (0.31)	75 (0.06)	0.56
Fatalities	0 (0)	0 (0)	0 (0)	0 (0)	-
Abdominal pain	17 (0.09)	0 (0)	3 (0.00)	1 (0)	0.92
Nausea	39 (0.20)	0 (0)	37 (0.05)	9 (0)	0.88
Nervous system disorder	322 ((1.71)	1 (72.88)	303 (0.43)	154 (0.14)	0.39
Fatalities	0 (0)	0 (0)	0 (0)	0 (0)	-
Headache	72 (0.38)	0 (0)	67 (0.09)	19 (0.01)	0.79
Psychiatric disorder	1542 (8.22)	0 (0)	174 (0.24)	73 (0.06)	<0.001
Fatalities	2 (0.01)	0 (0)	0 (0)	1 (0)	0.99
Agitation	34 (0.18)	0 (0)	6 (0)	1 (0)	0.84
Anxiety	165 (0.87)	0 (0)	35 (0.04)	7 (0)	0.46
Depression	82 (0.43)	0 (0)	7 (0)	4 (0)	0.66
Hallucinations	42 (0.22)	0 (0)	1 (0)	3 (0)	0.80
Nightmare	162 (0.86)	0 (0)	1 (0)	0 (0)	0.42
Suicidal ideation	62 (0.33)	0 (0)	2 (0)	2 (0)	0.72
Completed suicide	3 (0.01)	0 (0)	0 (0)	0 (0)	-
Respiratory, thoracic, and mediastinal disorders	125 (0.66)	0 (0)	587 (0.83)	528 (0.24)	0.85
Fatalities	0 (0)	0 (0)	0 (0)	0 (0)	-

Table 6. Psychiatric system organ class > high-level group term (HLGT). Order of information presented: raw number of suspected reports, standardised to prescribing level in parentheses, fatalities in square brackets. HLGT reported where at least one drug has $n > 1$ report. *p*-values reported where there were $n > 3$ reports. Supporting data can be found in Table S2.

HLGT	Montelukast	Beclomethasone	Salbutamol	*p*
Anxiety disorders and symptoms	275 (1.47)	58 (0.08)	22 (0.02)	0.28
Changes in physical activity	37 (0.20)	8 (0.01)	1 (0.00)	-
Cognitive and attention disorders and disturbances	6 (0.03)	1 (0.00)	0	-
Communication disorders and disturbances	15 (0.08)	1 (0.00)	0	-
Deliria (including confusion)	19 (0.10)	5 (0.01)	3 (0.00)	0.92
Depressed mood disorders and disturbances	162 (0.86)	17 (0.02)	8 (0.01)	0.45
Developmental disorders NEC	1 (0.01)	0	0	-
Dissociative disorders	5 (0.03)	0	0	-
Disturbances in thinking and perception	76 (0.41)	5 (0.01)	6 (0.01)	0.69
Impulse control disorders NEC	4 (0.02)	0	0	-
Manic and bipolar mood disorders and disturbances	6 (0.03)	0	0	-
Mood disorders and disturbances NEC	182 (0.97)	25 (0.04)	5 (0.00)	0.41
Personality disorders and disturbances in behaviour	144 (0.77)	14 (0.02)	1 (0.00)	-
Psychiatric and behavioural symptoms NEC	65 (0.35)	7 (0.01)	1 (0.00)	-
Psychiatric disorders NEC	26 (0.14)	0	6 (0.01)	-
Schizophrenia and other psychotic disorders	12 (0.06)	0	1 (0.00)	-
Sexual dysfunctions, disturbances, and gender identity disorders	0	0	1 (0.00)	-
Sleep disorders and disturbances	411 (2.19)	30 (0.04)	15 (0.01)	0.12
Somatic symptoms and related disorders	0	0	1 (0.00)	-
Suicidal and self-injurious behaviours NEC	96 (0.51) [2]	3 (0.00)	2 (0.00)	0.60

3. Discussion

3.1. Total ADRs and Fatalities

Zafirlukast was discontinued in 2018 due to commercial reasons [29]. This led to the drug not meeting the requirements for the inclusion criteria for the ADR/prescribing data collection as it had less than 100,000 R_x and was therefore excluded from the discussion addressing ADRs and fatalities.

Amongst all the drugs, montelukast had the highest ADR rate at 15.64 per 100,000 R_x, followed by beclomethasone at 3.37 and salbutamol at 1.2. Montelukast had significantly lower LLE compared to both beclomethasone and salbutamol (0.15 compared to 5.93 and 5.67) (Table 2). This implies greater promiscuity, and the data corroborates this, as montelukast potently inhibits two off-target proteins (Table 4). The highest rate for suspected drug involved fatalities across the drugs studied was shared by both montelukast and salbutamol (0.01 per 100,000 R_x).

3.2. Psychiatric ADRs

All SOC ADRs were found to not reach statistical significance except for psychiatric ADRs (Table 5). Montelukast ($p < 0.001$) provided the highest ADR rate at 8.22 per 100,000 R_x, which is logarithmically higher than the controls, beclomethasone, and salbutamol (0.24 and 0.06 per 100,000 R_x, respectively).

Further data mining beyond SOCs to HLGTs (Table 6) revealed emerging trends between montelukast and the controls but, in all cases, did not reach statistical significance ($p > 0.001$). Anxiety disorders and symptoms (275 vs. 70 reports for montelukast vs. controls respectively), depressed mood disorders (162 vs. 25 reports for montelukast vs. controls respectively), disturbances in thinking and perception (76 vs. 11 reports for montelukast vs. controls respectively), mood disorders (182 vs. 30 reports for montelukast vs. controls respectively), sleep disorders (411 vs. 45 reports for montelukast vs. controls respectively), and suicidal and self-injurious behaviours (96 vs. 5 reports for montelukast vs. controls respectively) showed clear trends, with higher reports for montelukast for both directly suspected ADRs and, when standardised to prescribing levels, compared to the controls. Furthermore, two fatalities within the suicidal and self-injurious category emerged for montelukast compared to the controls (zero for both salbutamol and beclomethasone).

A previous study compared the side effects of antidepressants and immune modulators including montelukast in human cell lines. Montelukast had a similar side effect profile to the atypical antidepressant, bupropion, which is a dopamine and norepinephrine reuptake inhibitor [30]. Montelukast impacts dopamine levels at a cellular level, despite not being pharmacologically relevant at the protein level based on a single dose C_{max} (Table 4). However, physiochemical data can only predict to a certain extent. Another study found that montelukast (at the recommended dose of 10 mg) was discovered in the cerebrospinal fluid (CSF) at a therapeutic dose. The central nervous system (CNS) was then evaluated afterwards to show that montelukast had penetrated the BBB significantly, which differs from the predicted BBB in Table 2 [31]. Furthermore a study of neuropsychiatric events in children, adolescents, and young adults taking montelukast found that montelukast accumulates in the CSF [32]. This accumulation at levels sufficient to impact the dopamine receptor (7.7 μM, Table 4) may potentially explain some of the psychiatric side effects via potential dysregulation of this neurotransmitter pathway.

3.3. Cardiac ADRs and Fatalities

Montelukast had a higher cardiac ADR rate at 0.13 per 100,000 R_x compared to both beclomethasone and salbutamol (Table 5) but did not reach statistical significance ($p = 0.98$). Suspected montelukast-induced heart palpitations were higher (0.12) in comparison with

beclomethasone and salbutamol (0.08 and 0.02 per 100,000 R_x), but again did not reach statistical significance ($p = 0.96$).

Montelukast is only usually added to asthma treatment if a patient has not responded to first-line treatment with salbutamol (prior to changes in NICE guidance in November 2024 [6]) with a regular low dose of inhaled corticosteroid (e.g., beclomethasone). Montelukast acts an alternative to an increased dose of inhaled corticosteroid, allowing management of symptoms via an alternative pharmacological pathway [33,34].

Montelukast has off-target interactions with adenosine A3 receptor and MAP kinase p38 alpha. The interaction with MAP kinase p38 alpha may be a cause of the cardiac effects. The p38 MAPK pathway plays an integral role in cardiac contractility and cardiac remodelling, and thus, inhibiting this protein may be a potential cause for the cardiac ADRs resulting with montelukast [35].

From a case report, cessation (withdrawal) of montelukast was considered a possible trigger in a 53-year-old male endurance athlete who presented with a two-week history of symptomatic ventricular ectopics, confirmed by ECG and 24 h tape. Other investigations were considered normal with no alternative identifiable causes for the arrhythmias which were resolved 24 h after re-starting the montelukast (please see Acknowledgements for more details).

Montelukast also inhibits adenosine A3 receptor, which has a significant role in myocardial infarction and atherosclerosis. Adenosine A3 receptors have cardioprotective characteristics which montelukast inhibits, which may make patients susceptible to deleterious cardiac effects [36].

3.4. Gastrointestinal Disorders and Site of Administration ADRs

Montelukast exceeded both beclomethasone and salbutamol's suspected gastrointestinal (GI) ADR rates per 100,000 R_x at 1.08 versus 0.31 and 0.06, respectively (Table 5). Montelukast caused a greater portion of GI ADRs which may be attributed to montelukast containing a lactose formulation, which certain patients may not respond well to.

There are directions for prescribers to assess whether the patient can tolerate this montelukast formulation by considering hereditary lactose conditions [37]. No fatalities were observed during this study for GI ADRs with non-serious ADRs reported. For abdominal pain, montelukast had a rate of 0.09 per 100,000 R_x whereas beclomethasone and salbutamol had a rate of 0. This is consistent with known side effects with montelukast (Table 1), therefore corroborating the validity of the approach using Yellow Card registry data [9].

3.5. Nervous System ADRs

Montelukast had the highest ADR rate at 1.71 per 100,000 R_x, whereas beclomethasone and salbutamol had lower rates (0.43 and 0.14, respectively). These ADRs share a similar background to psychiatric ADRs with BBB penetrability involved and affecting the dopamine axis [30,31]. Headaches are associated with montelukast at 0.38 per 100,000 R_x, and at 0.09 and 0.01 for salbutamol and beclomethasone, which was validated with comparison to the known side effects of montelukast [9].

4. Limitations

A limitation of this study is that zafirlukast was discontinued in 2018 resulting in only 1 year of prescribing data during the 5-year timeline of this study. The reason for the discontinuation of zafirlukast was reported as distribution issues rather than safety concerns of the drug.

The MHRA Yellow Card interactive Drug Analysis Profile presents all the suspected ADRs reported by both healthcare professionals and patients which is known to lead to a high degree of underreporting of side effects. This underreporting reduces the power of comparisons made across the drugs.

It should also be noted that some drugs are noticed by the public (e.g., montelukast) when announcements are made regarding potential side effects, and this may cause an uptick in reports generated, in comparison to a drug (e.g., salbutamol) which is a well-established first-line treatment that may not be reported at the same rate.

Montelukast is typically used as an adjunct when first-line asthma medications (SABA or SABA + ICS) are ineffective, often in combination with other drugs. Given that montelukast has a high plasma protein binding rate (99%), ADRs may be influenced by drug interactions (DDIs) not solely by the MoA of montelukast.

Causality does not need to be established before reporting to the Yellow Card scheme; therefore, the drug in question may not be the cause of the effect but rather other factors (polypharmacy, QoL, comorbidity), leading to the misrepresentation of the ADRs. Consequently, an assertive claim about the drug and which ADR it may cause, based only on the MHRA yellow card scheme, is not possible. However, trends and signal detection are possible.

United Kingdom ADRs used in this study were reported between January 2018 and November 2023, whilst the prescription data for England only was available from August 2018 to September 2023. This does not affect the standardisation of drugs as the time frame remains consistent with time lags associated with reporting ADRs but may not appropriately reflect the full drug prescriptions across the full 5 years of the study (84% of UK prescribing statistics based on population vs. 100% of the reported suspected ADRs across the UK).

5. Methods

5.1. Method Databases

The Electronic Medicines Compendium (EMC) and the Chemical Database of bioactive molecules with drug-like properties European Molecular Biology Laboratory (ChEMBL), DrugBank, and PubChem databases (all publicly available access without subscription) were used to identify the physiochemical properties, pharmacokinetics, and pharmacology data of montelukast, zafirlukast, beclomethasone, and salbutamol [37–40].

5.2. Physiochemical Properties

The physicochemical properties included molecular weight, pK_a, ^{t}PSA, hydrogen bond donors and acceptors, $clogD_{7.4}$, whether it is a P-glycoprotein substrate, and the $clog_{10}P$ [28]. The pIC_{50} was calculated using the median IC_{50} of the target *Homo sapien* protein for each respective drug. The lipophilic ligand efficacy (LLE) was calculated as follows: $LLE = pIC_{50} - clog_{10}P$ (Table 2) [40].

5.3. Pharmacokinetic Properties

EMC, DrugBank, PubChem, ChEMBL and the wider literature were used to find pharmacokinetic data, by searching for the "drug name" and the "parameter required" (Table 3) [37–46].

5.4. Pharmacological Properties

The ChEMBL database was used to collect the human single protein target bioactivity data for montelukast, zafirlukast, beclomethasone and salbutamol [40]. The median IC_{50} values were used to determine the pIC_{50} value (Table 4).

5.5. Prescribing Data

Prescription data in primary care across England was curated from OpenPrescribing (August 2018 until September 2023) [47]. OpenPrescribing converts anonymized NHS England prescription data, issued by GPs and released monthly, into interpretable infographics. The "Find a drug" search tool was used and a search made using the active drug name/BNF code. Where multiple search returns were identified, the individual .csv files were combined and the sum of items issued during the timeframe were calculated and extracted without adjustment for population changes during these years.

Prescription items (R_x) were collated to standardise the suspected ADRs per 100,000 R_x to factor in variations in prescription rates amongst the medications. A minimum of 100,000 R_x between 2018 and 2023 was an additional inclusion criterion.

5.6. Adverse Drug Reactions

Suspected ADR data was data-mined from the Medicines and Healthcare products Regulatory Authority (MHRA) Yellow Card interactive Drug Analysis Profile (iDAP) for the United Kingdom (England, Scotland, Wales, and Northern Ireland). Dates selected were January 2018 to November 2023 for single active constituents only [48]. System organ classes (SOC) with significant ADR rates across the medications and fatalities were selected. The selection criteria were based on >50 ADR reports per year of the study and ≥1 fatality for the SOCs that may be related to a pharmacological action. General disorders and administration site conditions, infections and infestations, injury, poisoning and procedural complications, investigations, product issues, social circumstances, surgical and medical procedures were excluded, and only general disorders and administration sites would have been eligible for inclusion otherwise. Additionally, SOC cardiac disorders were selected due to a case report communication relating to montelukast withdrawal.

The ADR data required standardisation to allow for comparisons between the different drugs. ADRs per 100,000 R_x is a standard approach in signal hypothesis generation [40,49–54]. The approach is as follows:

$$(n' \text{ ADRs}/n'' \text{ } R_x) \times 100{,}000 \text{ } R_x = n \text{ ADRs}/100{,}000 \text{ } R_x. \quad (1)$$

Drugs were compared in terms of ADR SOCs (Table S1, Table 5 and Figure 2) to determine statistically significant signals and where $p < 0.001$, high-level group terms (HLGT) were additionally explored (Table S2, Table 6 and Figure 3).

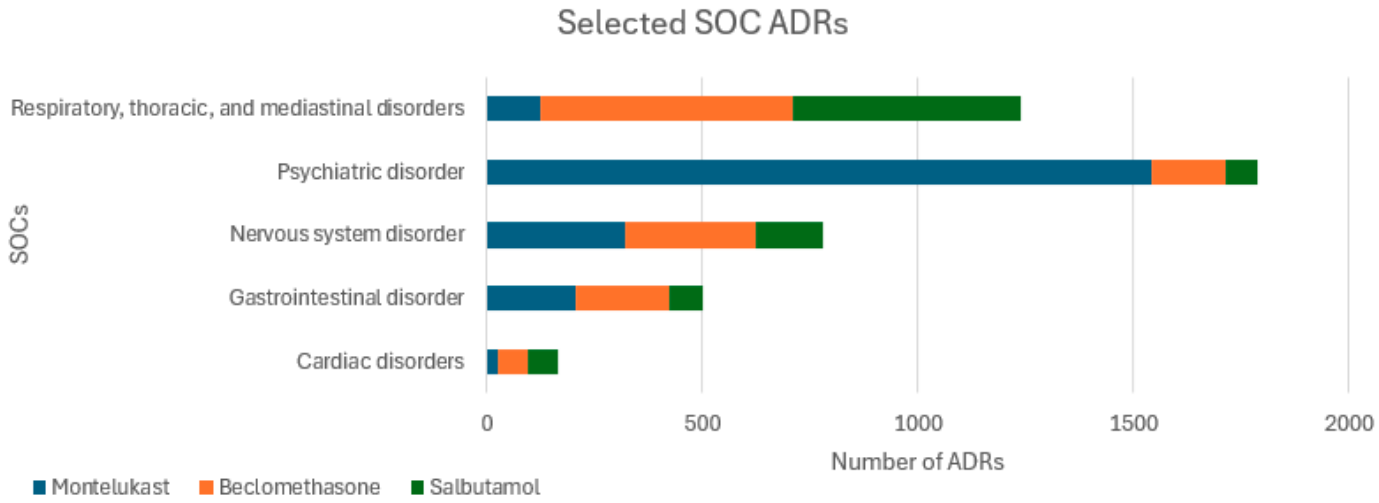


Figure 2. Stratified bar chart of selected SOC ADRs for the three drugs studied.

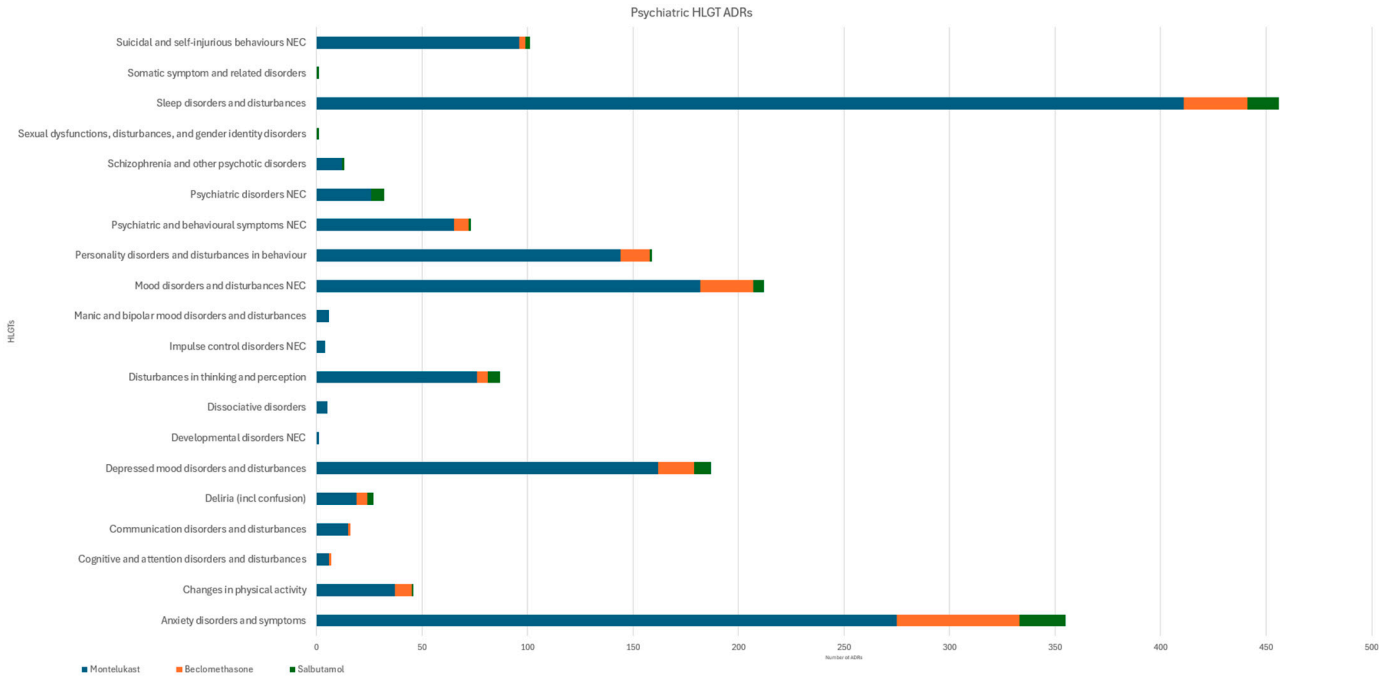


Figure 3. Stratified bar chart of psychiatric HLGT ADRs for the three drugs studied.

5.7. Ethics

Due to the use of fully anonymized ADR reports and prescribing data from publicly available databases, ethics approval from the sub-ethics committee (School of Pharmacy) was not required.

6. Conclusions

Based on the data observed in this study, montelukast has shown a range of suspected ADRs, ranging from cardiac, gastrointestinal, nervous system, and anticipated, rare but important, psychiatric side effects. However, it should be noted that individual risk factors are not considered within the limitations of the data source, which may have a bearing on montelukast's risk profile. Furthermore, the known risks of first-line drugs such as beclomethasone may lead to underreporting of ADRs in more established drugs, which may place an undue emphasis on montelukast's risks.

The physiochemical data showed a poor prediction of the BBB penetration of montelukast, but evidence from the literature demonstrated that montelukast does penetrate the BBB and accumulate in the CSF, which may have a bearing on nervous and psychiatric ADRs associated with montelukast.

The research approach employed in this study was validated with the analysis of known montelukast ADRs. In particular, the elevated levels of nervous system and psychiatric disorders reported with montelukast are consistent with the MHRA field notice about adverse effects associated with montelukast [17]. Montelukast has been associated with mood changes, depression, aggression, hallucinations, and suicidal thoughts, and this work further supports these neuropsychiatric findings and a potential pharmacological rationale via interaction with the dopamine GPCR axis through CSF accumulation.

Cardiac ADRs associated with montelukast have a tentative relationship with the pharmacological profile, which supports the inhibition of off-target proteins that have an association with cardiac ADRs.

The research demonstrated a new perspective that combines pharmacovigilance registries and chemical–pharmacological data to understand the potential mechanism of the ADRs of LTRAs.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/pharma4030018/s1, Table S1. Raw system organ class ADRs/fatalities and relative to 100,000 R_x (indicated by (s)) and Table S2. Raw Higher Level Group Terms (HLGTs) ADRs/fatalities and relative to 100,000 R_x (indicated by (s)).

Author Contributions: Conceptualization, A.M.J., C.H.; Methodology, A.M.J., C.H., M.K.; Formal analysis, M.K.; Data curation, M.K.; Investigation, M.K.; Visualization, M.K.; Writing—original draft, A.M.J., C.H., M.K.; Writing—review and editing, A.M.J., C.H., M.K.; Supervision, A.M.J., C.H.; Project administration, A.M.J. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The original contributions presented in this study are included in the article/Supplementary Materials. Further inquiries can be directed to the corresponding authors.

Acknowledgments: The authors thank MHRA, OpenPrescribing, and ChEMBL for the publicly accessible curated open-access data that was used in this study. Information from the case report was based on personal communication to C.H. University of Birmingham, 17th September 2025, further details upon request.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Asthma and Lung UK. What is Asthma? | Asthma + Lung UK. Available online: https://www.asthmaandlung.org.uk/conditions/asthma/what-asthma#:~:text=Asthma%20is%20a%20very%20common (accessed on 10 December 2023).
2. NICE. What Is the Prevalence of Asthma? NICE. May 2022. Available online: https://cks.nice.org.uk/topics/asthma/background-information/prevalence/ (accessed on 10 December 2023).
3. BTS/NICE/SIGN Joint Guideline on Asthma: Diagnosis, Monitoring and Chronic Asthma Management. Available online: https://www.brit-thoracic.org.uk/quality-improvement/guidelines/asthma/ (accessed on 12 June 2024).
4. Mukherjee, M.; Stoddart, A.; Gupta, R.P.; Nwaru, B.I.; Farr, A.; Heaven, M.; Fitzsimmons, D.; Bandyopadhyay, A.; Aftab, C.; Simpson, C.R.; et al. The epidemiology, healthcare and societal burden and costs of asthma in the UK and its member nations: Analyses of standalone and linked national databases. *BMC Med.* **2016**, *14*, 113. [CrossRef]
5. NICE. Available online: https://www.nice.org.uk/guidance/ng80/resources/algorithm-f-pharmacological-treatment-of-chronic-asthma-in-adults-aged-17-and-over-pdf-4656176754 (accessed on 12 June 2024).
6. NICE. Algorithm C: Pharmacological Management of Asthma in People Aged 12 Years and Over. Available online: https://www.nice.org.uk/guidance/ng245/resources/algorithm-c-pharmacological-management-of-asthma-in-people-aged-12-years-and-over-bts-nice-pdf-13556516367 (accessed on 10 September 2025).
7. Sampson, A.; Holgate, S. Leukotriene modifiers in the treatment of asthma. *BMJ* **1998**, *316*, 1257–1258. [CrossRef]
8. Coleman, J.J.; Pontefract, S.K. Adverse drug reactions. *Clin. Med.* **2016**, *16*, 481–485. [CrossRef] [PubMed]
9. King, C.; McKenna, A.; Farzan, N.; Vijverberg, S.J.; van der Schee, M.P.; Maitland-van der Zee, A.H.; Arianto, L.; Bisgaard, H.; BØnnelykke, K.; Berce, V.; et al. Pharmacogenomic associations of adverse drug reactions in asthma: Systematic review and research prioritisation. *Pharmacogenom. J.* **2020**, *20*, 621–628. [CrossRef]
10. Paljarvi, T.; Forton, J.; Luciano, S.; Herttua, K.; Fazel, S. Analysis of Neuropsychiatric Diagnoses After Montelukast Initiation. *JAMA Netw. Open* **2022**, *5*, e2213643. [CrossRef]
11. Kim, J.W.; Kim, M.; Seo, M.S.; Shin, J.Y. Risk of neuropsychiatric adverse events associated with montelukast use in children and adolescents: A population-based case-crossover study. *BMJ Paediatr. Open* **2024**, *8*, e002483. [CrossRef]
12. Wintzell, V.; Brenner, P.; Halldner, L.; Rhedin, S.; Gong, T.; Almqvist, C. Montelukast Use and the Risk of Neuropsychiatric Adverse Events in Children. *JAMA Pediatr.* **2025**, *179*, 418–427. [CrossRef] [PubMed]
13. Watson, S.; Kaminsky, E.; Taavola, H.; Attalla, M.; Yue, Q.Y. Montelukast and Nightmares: Further Characterisation Using Data from VigiBase. *Drug Saf.* **2022**, *45*, 675–684. [CrossRef] [PubMed]
14. Lee, Y.J.; Kim, C.K. Montelukast use over the past 20 years: Monitoring of its effects and safety issues. *Clin. Exp. Pediatr.* **2020**, *63*, 376–381. [CrossRef]

15. Umetsu, R.; Tanaka, M.; Nakayama, Y.; Kato, Y.; Ueda, N.; Nishibata, Y.; Hasegawa, S.; Matsumoto, K.; Takeyama, N.; Iguchi, K.; et al. Neuropsychiatric Adverse Events of Montelukast: An Analysis of Real-World Datasets and drug-gene Interaction Network. *Front. Pharmacol.* **2021**, *12*, 764279. [CrossRef]
16. Lo, C.W.H.; Pathadka, S.; Qin, S.X.; Fung, L.W.Y.; Yan, V.K.C.; Yiu, H.H.E.; Bloom, C.I.; Wong, I.C.K.; Chan, E.W.Y. Neuropsychiatric events associated with montelukast in patients with asthma: A systematic review. *Eur. Respir. Rev.* **2023**, *32*, 230079. [CrossRef] [PubMed]
17. Montelukast (Singulair): Reminder of the Risk of Neuropsychiatric Reactions. Available online: https://www.gov.uk/drug-safety-update/montelukast-singulair-reminder-of-the-risk-of-neuropsychiatric-reactions (accessed on 16 December 2023).
18. Yao, T.C.; Huang, J.L.; Wu, C.S.; Lu, H.H.S.; Chang, Y.C.; Chen, W.Y.; Kao, H.F.; Wu, A.C.; Tsai, H.J. Comparative Risk of Neuropsychiatric Adverse Events Associated With Leukotriene-Receptor Antagonists Versus Inhaled Corticosteroids. *J. Allergy Clin. Immunol. Pract.* **2025**, *13*, 903–911.e5. [CrossRef] [PubMed]
19. Kovesi, T. Neuropsychiatric side effects of montelukast. *J. Pediatr.* **2019**, *212*, 248. [CrossRef]
20. Mou, Y.; Song, Q.; Zhao, C.; Fang, H.; Ren, C.; Song, X. Meta-analysis of the relationship between montelukast use and neuropsychiatric events in patients with allergic airway disease. *Heliyon* **2023**, *9*, e21842. [CrossRef]
21. Marques, C.F.; Marques, M.M.; Justino, G.C. The mechanisms underlying montelukast's neuropsychiatric effects-new insights from a combined metabolic and multiomics approach. *Life Sci.* **2022**, *310*, 121056. [CrossRef] [PubMed]
22. Giangreco, N.P.; Tatonetti, N.P. A database of pediatric drug effects to evaluate ontogenic mechanisms from child growth and development. *Med.* **2022**, *3*, 579–595.e7. [CrossRef]
23. Costello, J.F. Leukotriene Antagonists. *Pulm. Pharamacol. Ther.* **1998**, *11*, 393–395. [CrossRef]
24. Wakabayashi, T.; Nakatsuji, T.; Kambara, H.; Niinomi, I.; Oyama, S.; Inada, A.; Ueno, S.; Uchida, M.; Iwanaga, K.; Iida, T.; et al. Drug-induced Neuropsychiatric Adverse Events Using Post-Marketing Surveillance. *Curr. Rev. Clin. Exper. Pharmacol.* **2022**, *17*, 144–148. [CrossRef]
25. de Oliveira Cardoso, J.; Oliveira, R.V.; Lu, J.B.; Desta, Z. In Vitro Metabolism of Montelukast by Cytochrome P450s and UDP-Glucuronosyltransferases. *Drug Metab. Dispos.* **2015**, *43*, 1905–1916. [CrossRef]
26. Balani, S.K.; Xu, X.; Pratha, V.; Koss, M.A.; Amin, R.D.; Dufresne, C.; Miller, R.R.; Arison, B.H.; Doss, G.A.; Chiba, M.; et al. Metabolic profiles of montelukast sodium (Singulair), a potent cysteinyl leukotriene1 receptor antagonist, in human plasma and bile. *Drug Metab. Dispos.* **1997**, *25*, 1282–1287. [PubMed]
27. Filppula, A.M.; Laitila, J.; Neuvonen, P.J.; Backman, J.T. Reevaluation of the microsomal metabolism of montelukast: Major contribution by CYP2C8 at clinically relevant concentrations. *Drug Metab. Dispos.* **2011**, *39*, 904–911. [CrossRef]
28. Jones, L.; Jones, A.M. Suspected adverse drug reactions of the type 2 antidiabetic drug class dipeptidyl-peptidase IV inhibitors (DPP4i): Can polypharmacology help explain? *Pharmacol. Res. Perspect.* **2022**, *10*, e01029. [CrossRef]
29. Zafirlukast discontinued. Prescribing Advice for GPs. Available online: https://www.prescriber.org.uk/2018/04/zafirlukast-discontinued/comment-page-1/#:~:text=Commercial%20reasons%20are%20cited%20for (accessed on 16 January 2024).
30. Michael, J.; Bessa de Sousa, D.; Conway, J.; Gonzalez-Labrada, E.; Obeid, R.; Tevini, J.; Felder, T.; Hutter-Paier, B.; Zerbe, H.; Paiement, N.; et al. Improved Bioavailability of Montelukast through a Novel Oral Mucoadhesive Film in Humans and Mice. *Pharmaceutics* **2020**, *13*, 12. [CrossRef] [PubMed]
31. Marschallinger, J.; Schäffner, I.; Klein, B.; Gelfert, R.; Rivera, F.J.; Illes, S.; Grassner, L.; Janssen, M.; Rotheneichner, P.; Schmuckermair, C.; et al. Structural and functional rejuvenation of the aged brain by an approved anti-asthmatic drug. *Nat. Commun.* **2015**, *6*, 8466. [CrossRef] [PubMed]
32. Park, J.S.; Cho, Y.J.; Yun, J.Y.; Lee, H.J.; Yu, J.; Yang, H.J.; Suh, D.I. Leukotriene receptor antagonists and risk of neuropsychiatric events in children, adolescents, and young adults: A self-controlled case series. *Eur. Respir. J.* **2022**, *60*, 2102467. [CrossRef]
33. Henderson, I.; Caiazzo, E.; McSharry, C.J.; Guzik, T.; Maffia, P.M. Why do some asthma patients respond poorly to glucocorticoid therapy? *Pharmacol. Res.* **2020**, *160*, 105189. [CrossRef]
34. Paggiaro, P.; Bacci, E. Montelukast in asthma: A review of its efficacy and place in therapy. *Ther. Adv. Chronic Dis.* **2010**, *2*, 47–58. [CrossRef] [PubMed]
35. Romero-Becerra, R.; Santamans, A.M.; Folgueira, C.; Sabio, G. p38 MAPK Pathway in the Heart: New Insights in Health and Disease. *Int. J. Mol. Sci.* **2020**, *21*, 7412. [CrossRef]
36. Nishat, S.; Khan, L.A.; Ansari, Z.M.; Basir, S.F. Adenosine A3 Receptor: A promising therapeutic target in cardiovascular disease. *Curr. Cardiol. Rev.* **2016**, *12*, 18–26. [CrossRef]
37. Electronic Medicines Compendium (EMC). Available online: https://www.medicines.org.uk/emc/ (accessed on 10 December 2023).
38. Wishart, D.S.; Knox, C.; Guo, A.C.; Shrivastava, S.; Hassanali, M.; Stothard, P.; Chang, Z.; Woolsey, J. Drugbank: A comprehensive resource for in silico drug discovery and exploration. *Nucleic Acids Res.* **2006**, *34*, D668–D672. [CrossRef]
39. Kim, S.; Chen, J.; Cheng, T.; Gindulyte, A.; He, J.; He, S.; Li, Q.; Shoemaker, B.A.; Thiessen, P.A.; Yu, B.; et al. PubChem 2023 update. *Nucleic Acids Res.* **2023**, *51*, D1373–D1380. [CrossRef]
40. ChEMBL Database. Available online: https://www.ebi.ac.uk/chembl/ (accessed on 16 December 2023).

41. Calhoun, W.J. Summary of Clinical Trials with Zafirlukast. *Am. J. Respir. Crit. Care Med.* **1998**, *157*, S238–S246. [CrossRef]
42. Dhaliwal, A.; Bajaj, T. Zafirlukast. PubMed. 2023. Available online: https://www.ncbi.nlm.nih.gov/books/NBK557844/#:~:text=Zafirlukast%20belongs%20to%20the%20leukotriene (accessed on 10 September 2025).
43. SciFinder. Available online: https://scifinder-n.cas.org/searchDetail/reference/6543cd23f2a71734588a5251/referenceDetails (accessed on 10 December 2023).
44. Roberts, J.K.; Moore, C.D.; Ward, R.M.; Yost, G.S.; Reilly, C.A. Metabolism of Beclomethasone Dipropionate by Cytochrome P450 3A Enzymes. *J. Pharmacol. Exp. Ther.* **2013**, *345*, 308–316. [CrossRef]
45. Hindle, M.; Chrystyn, H. Determination of the relative bioavailability of salbutamol to the lung following inhalation [see comments]. *Br. J. Clin. Pharmacol.* **1992**, *34*, 311–315. [CrossRef]
46. Kruizinga, M.D.; Birkhoff, W.A.; van Esdonk, M.J.; Klarenbeek, N.B.; Cholewinski, T.; Nelemans, T.; Dröge, M.J.; Cohen, A.F.; Zuiker, R.G. Pharmacokinetics of intravenous and inhaled salbutamol and tobramycin: An exploratory study to investigate the potential of exhaled breath condensate as a matrix for pharmacokinetic analysis. *Br. J. Clin. Pharmacol.* **2020**, *86*, 175–181. [CrossRef]
47. Open Prescribing. Available online: https://openprescribing.net/ (accessed on 20 October 2023).
48. Medicines and Healthcare Products Regulatory Agency. Available online: https://yellowcard.mhra.gov.uk/idaps (accessed on 10 September 2025).
49. Ferro, C.J.; Solkhon, F.; Jalal, Z.; Al-Hamid, A.M.; Jones, A.M. Relevance of physicochemical properties and functional pharmacology data to predict the clinical safety profile of direct oral anticoagulants. *Pharmacol. Res. Perspect.* **2020**, *8*, e00603. [CrossRef]
50. Matharu, K.; Chana, K.; Ferro, C.; Jones, A.M. Polypharmacology of clinical sodium glucose co-transport protein 2 inhibitors and relationship to suspected adverse drug reactions. *Pharmacol. Res. Perspect.* **2021**, *9*, e00867. [CrossRef]
51. Sandhu, D.; Antolin, A.A.; Cox, A.R.; Jones, A.M. Identification of different side effects between PARP inhibitors and their polypharmacological multi-target rationale. *Brit. J. Clin. Pharmacol.* **2022**, *88*, 742–752. [CrossRef]
52. Salim, H.; Jones, A.M. Angiotensin II Receptor Blockers (ARBs) and Manufacturing Contamination: A Retrospective National Register Study into suspected associated adverse drug reactions. *Brit. J. Clin. Pharmacol.* **2022**, *88*, 4812–4827. [CrossRef]
53. Yousaf, H.; Jones, A.M. The Relationship Between Suspected Adverse Drug Reactions Of HMG-Coa Reductase Inhibitors and Polypharmacology Using a National Registry Approach. *MedRxiv* **2024**. [CrossRef]
54. Phillips, B.; Evans, I.; Skerrett, V.; Jones, A.M. United Kingdom National Register Study of Anti-Epileptic Medications: Suspected Foetal Congenital and Pregnancy-Associated Side Effects. *MedRxiv* **2024**. [CrossRef]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.