



# Adverse drug reactions of leukotriene receptor antagonists in children with asthma: a systematic review

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## ABSTRACT

**Background** Asthma is the most common chronic condition of childhood. Leukotriene receptor antagonists (LTRAs) are included in international guidelines for children and young people (CYP), but there have been highly publicised concerns about potential adverse effects. The aim was to identify and understand the reported frequency of adverse drug reactions (ADRs) attributed to LTRAs in CYP with asthma.

**Methods** Embase, MEDLINE, PubMed and CINAHL were searched up to October 2020. Reference lists of eligible papers were manually screened. Eligible studies identified adverse events attributed to an LTRA in individuals aged between 0 and 18 years diagnosed with asthma. Four different tools were used to assess risk of bias or quality of data to accommodate the papers assessed.

**Results** The search identified 427 papers after deduplication; 15 were included (7 case reports, 7 case-controlled or cohort studies and 1 randomised control trial (RCT)). 7012 patients were recorded, of which 6853 received an LTRA. 13 papers examined the ADRs attributed to montelukast, one to pranlukast and one to unspecified LTRAs. After language standardisation, 48 ADRs were found, 20 of which were psychiatric disorders. Across all studies, the most commonly reported ADRs were 'anxiety', 'sleep disorders' and 'mood disorders'. The frequency of ADRs could be calculated in seven of the eight studies.

Applying standardised frequency terms to the prospective studies and RCT, there were 14 'common' and 'uncommon' ADRs. 'Common' ADRs included 'agitation/hyperactivity/irritability/nervousness', 'aggression' and 'headache'.

The case reports showed a similar pattern, describing 46 different ADRs experienced by a total of eight patients.

**Conclusions** LTRAs have a wide range of suspected ADRs in CYP, predominantly gastrointestinal and neuropsychiatric disorders. Careful monitoring of CYP with asthma is required, both to assess and manage ADRs and to step treatment down when clinically stable.

**PROSPERO registration number** CRD42020209627.

## INTRODUCTION

Asthma is a disease of airway inflammation and bronchoconstriction. It is the most common chronic disease of childhood globally, affecting more than 338 million children globally.<sup>1,2</sup> The UK has the highest prevalence of childhood asthma symptoms in the world,

## What is known about the subject?

- Asthma is the most common chronic condition of childhood globally.
- Leukotriene receptor antagonists are internationally recommended as a step-up therapy for patients with asthma whose asthma is not controlled by inhaled corticosteroids.
- There have been highly publicised concerns and the addition of warnings to the packaging regarding leukotriene receptor antagonists adverse drug reactions.

## What this study adds?

- Leukotriene receptor antagonists have a wide range of suspected adverse drug reactions in children.
- Neuropsychiatric and gastrointestinal adverse drug reactions are the most common.

with the National Health Service spending around 1 billion pounds each year on asthma care.<sup>3,4</sup> Globally, the prevalence of asthma has been steadily increasing, and as a result, so has the prescribing of anti-asthma medication, with management guided by national and international guidelines.<sup>2,5-7</sup>

Leukotriene receptor antagonists (LTRAs) are a class of drugs used as a preventative treatment for asthma and are usually prescribed as an additional therapy for patients whose acute symptoms and attacks remain uncontrolled by inhaled corticosteroids.<sup>6-8</sup> Montelukast, the originator drug in this class, has also been separately licenced for allergic rhinitis in some nations.<sup>9-11</sup> Initially licenced in 1998, montelukast was the 16th most prescribed medication in 2020 globally.<sup>12,13</sup>

Medications come with potential harms such as adverse drug reactions (ADRs), defined as 'an unwanted or harmful reaction which occurs after administration of drugs' and 'is suspected or known to be due to the drug(s)'.<sup>14</sup> In March 2020 montelukast was

marked with a boxed warning by the US Food and Drug Administration (FDA) and other agencies, warning of the potential severity of adverse events attributed to the labelled drug.<sup>15</sup> There was particular concern regarding significant neuropsychiatric events associated with this drug. These included suicidal thoughts and actions, depression and sleeping problems.<sup>15–19</sup>

This systematic review aims to identify types of ADRs reported in the medical literature for children and young people (CYP) who use LTRAs and provide estimates of the frequency of these suspected ADRs.

## AIMS

The primary aim was to identify and understand the frequency of ADRs attributed to LTRA in CYP with asthma.

## METHODS

The protocol for this review was registered, a priori, in the International Prospective Register of Systematic Reviews. The review is reported as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and follows the guidance recommended in other methodological papers.<sup>20</sup>

### Eligibility criteria

All primary research study designs including case reports, randomised control trials (RCT) and cohort studies were eligible. Narrative reviews were excluded. Eligible studies contained patients aged 0–18 years who were taking an LTRA as a preventative therapy for asthma, and the frequency of ADRs (number of patients who presented with a described ADR in a defined cohort) was described in the study report. For case reports, this criteria was understood as the presentation of a novel ADR following the administration of an LTRA. Adverse events as a consequence of LTRA non-prescribed dose (eg, overdose) were also excluded. Studies in which the evaluation of ADRs was not the primary objective, and which stated that the ADRs presented were not significantly different from the placebo were excluded as the attribution of the ADR to the LTRA could not be confirmed. Studies which contained both adult (18+ years) and paediatric data were eligible only if the relevant data (ADRs in CYP) were recorded separately from results in adults. Human studies in any language and with any publication date were included.

### Search strategy and study selection

In September 2020, we searched MEDLINE, PubMed, Embase and CINAHL using a combination of Medical Subject Headings (MeSH) and free-text subject headings to include the research question (see online supplemental table S1, for complete search strategy). The primary author (EGD) screened the titles and abstracts of all identified studies before comparing the full texts

of the remaining studies with the eligibility criteria. This process was repeated independently by the second author (CEMR-G) in October 2020. Subsequently the authors finalised the eligible studies; the senior author (DBH) resolved disagreements between the authors at the full-text stage. Using the same eligibility criteria, the reference lists of all eligible papers were additionally manually screened.

### Quality assessment

RCT<sup>21</sup> (1/15), cohort or case-control studies<sup>22</sup> (7/15) and case studies<sup>23</sup> (7/15) were assessed for risk of bias or quality of data using appropriate assessment tools (online supplemental tables S2–S4).

### Data extraction and synthesis

Data were extracted from the eligible studies into Microsoft Excel (Office 2016) (tables 1 and 2). When studies were reported in multiple publications, information (such as study design, placebo status, etc) was collected across the multiple publications to maximise the information available. In these cases, data duplication or accidental non-inclusion was avoided by comparing the study design, authors, study date and participant number across the publications to ensure the data originated from the same study. In cases where studies presented ADR data as percentages of a defined population, the numerical incidence of each adverse event was calculated.

Following data extraction, the language used to describe the reported ADRs was standardised to facilitate data analysis and avoid ADR ambiguity. Medical Dictionary for Regulatory Activities (MedDRA) terminology, defined as ‘a rich and highly specific standardised medical terminology to facilitate sharing of regulatory information internationally for medical products used by humans’, was assigned to each ADR term reported to ensure a universal understanding of the given ADR term.<sup>24</sup> Where the intention of the term used to describe an ADR was ambiguous, three authors (EGD, DBH and IS) independently assigned MedDRA terms based on the context of the reported ADR in question, before collectively confirming the terms (online supplemental table S5). Similar or matching controlled language ADR terms were subsequently grouped before being categorised by class organ system. Adverse events categorised under multiple MedDRA class organ systems were assigned to a single class organ system. Again, this process was conducted independently by the three authors (EGD, DBH and IS) before consensus was reached (online supplemental table S6).

Additionally, definitions of frequencies were described using Summary of Product Characteristics (SmPC) guidelines—an internationally used standardised regulatory framework.<sup>25</sup>

The frequencies of these standardised and grouped terms were collated (table 2). Frequency data from the prospective studies/RCT (table 3) and case reports (table 4) were additionally examined separately.

**Table 1** Eligible studies

Paper	The study		Leukotriene receptor antagonist			Participant characteristics (as presented in study)	Leukotriene receptor antagonist		Length of drug administration prior to ADR presentation	Other drugs administered by patients
	Year	Type of study	Patients (of relevant age)	Patients administered the LTRA	Age of patients		LTRA administered	Dose information given		
<b>Lenney</b> <sup>26</sup>	2013	Randomised, double-blind, placebo controlled, parallel study	63	21	6–14 years 11 months	40 males, 23 females (whole study)	Montelukast	5 mg/day	0–48 weeks	Inhaled fluticasone propionate 100 µg two times per day.
<b>Ammarr</b> <sup>29</sup>	2018	Prospective cohort study	56	56	2–17 years	Not specified	Montelukast	Not specified	1–24 weeks	Inhaled steroids.
<b>Ghosh</b> <sup>27</sup>	2006	Prospective cohort study	50	50	3–11 years	28 males, 22 females	Montelukast	3–4 years 4 mg, >4 years 5 mg	Not specified	Salbutamol or terbutaline, used when needed.
<b>Kukreja</b> <sup>28</sup>	2004	Prospective cohort study	881	881	6–14 years	573 males, 308 females	Montelukast	5 mg/day	0–30 days	Short acting inhaled beta-2-agonists, used 'as needed'.
<b>Arnold</b> <sup>45</sup>	2020	Retrospective cohort study	312	312	age 6 (5–8) years (median (IQR))	55% male, 45% female	Montelukast	(0.5–17.8 mg/kg/day)	Not specified	Not specified.
<b>Benard</b> <sup>46</sup>	2017	Retrospective cohort study	223	106	1–17 years	66 male, 40 female (case). 66 Caucasian, 21 North African, 4 black, 3 Asian, 3 East Indian, 3 Hispanic, 6 inter-racial/other (case).	Montelukast	2 unknown, 53 4 mg/day, 47 5 mg/day, 4 10 mg/day	Not specified	Not specified.
<b>Erdem</b> <sup>47</sup>	2015	Retrospective cohort study	1024	1024	Not specified ('children')	Not specified	Not specified	Not specified	Not specified	Not specified.
<b>Glocker-Lauf</b> <sup>48</sup>	2018	Matched, nested case-control study	4395	4395	5–18 years	1874/3497 female (control), 476/898 female (case).	Montelukast	Not specified	Not specified	'Asthma Maintenance Medication' other than an LTRA.
<b>Kobayashi</b> <sup>31</sup>	2003	Case report	1	1	17 years	Japanese male	Pranlukast	450 mg/day	13 months	Theophylline 400 mg/day.
<b>Kocoyigit</b> <sup>49</sup>	2013	Case report	1	1	13 years	Male	Montelukast	Not specified	24–36 hours	Salbutamol, formoterol and budesonide.

Continued

Table 1 Continued

Paper	The study			Leukotriene receptor antagonist			Other drugs			
	Year	Type of study	Patients (of relevant age)	Patients administered the LTRA	Age of patients	Participant characteristics (as presented in study)		LTRA administered	Dose information given	Length of drug administration prior to ADR presentation
<b>Byrne</b> <sup>50</sup>	2012	Case report	1	1	9 years	Caucasian male	Montelukast	5 mg/day	2.5 years	Beclomethasone inhaler, 50 mcg, 1 puff two times per day.
<b>Montoro De Francisco</b> <sup>30</sup>	2015	Case report	1	1	7 years	Male	Montelukast	4 mg/day	12 hours	Not specified.
<b>Scholz</b> <sup>51</sup>	2019	Case report	1	1	11 years	Male	Montelukast	Not specified	4 months	Salbutamol and salmeterol/fluticasone.
<b>Skillman</b> <sup>52</sup>	2011	Case report	2	2	1. 4 years 2. 6 years	1. Male 2. Hispanic female	Montelukast	1. 5 mg/day 2. 4 mg/day then 5 mg/day	1. Since starting nebulised every 4–6 hours, cetirizine 5 mg daily. 2. Since does child's sixth birthday	1. Albuterol 2.5 mg nebulised every 4–6 hours, cetirizine 5 mg daily. 2. Fluticasone oral inhaler 44 mcg two times per day, cetirizine 5 mg.
<b>Star</b> <sup>53</sup>	2011	Case report	1	1	Teenage	Male	Montelukast	Not specified	Not specified	Escitalopram which was later changed to venlafaxine and risperidone.

ADR, adverse drug reaction; LTRA, leukotriene receptor antagonist.

Table 2 Primary outcome data

COS	Papers containing an ADR in COS (/15)		Patients with suspected ADR in COS*	Patients given LTRA in COS*	Characterised ADRs reported (/48)	Papers containing ADR (/15)	Patients given LTRA	Patients with suspected ADR	ADR terms given in paper (/73)
	10	5899							
Psychiatric disorders					Aggression	2	162	18	Aggression
					Agitation/hyperactivity/irritability/nervousness	7	5869	64	Agitation; agitation/hyperactivity; irritability; nervousness; nervousness/agitation
					Anxiety	6	4561	450	Anxiety; separation anxiety
					Behaviour disorders	2	108	5	Behaviour problems; tantrums
					Bruxism	1	1	1	Bruxism
					Depression	2	107	2	Depression; depressive state
					Disorientation	1	2	1	Disorientated when waking
					Disturbance in attention	1	1	1	Reduced attention span
					Hallucination	2	1025	5	Hallucination
					Insomnia	3	163	5	Insomnia
					Mood disorders	3	4502	172	Change in mood; mood; mood swings; personality
					Nyctophobia	1	1024	4	Nyctophobia
					Restlessness	1	1	1	Restlessness
					Schizophrenia	1	4395	13	Schizophrenia
					Substance-related and addictive disorders	1	4395	99	Substance-related
					Sleep disorders	5	5528	245	Change in sleeping patterns; difficulty falling asleep without parent; sleep disorder/depression; sleep disturbance; sleeping badly
					Sleep terror	3	164	10	Crying when waking; nightmares
				Somnambulism	2	3	2	Sleepwalking	
				Suicidal ideation	1	1	1	Suicidal ideation	
				Thinking abnormal	1	1	1	Felt he was going crazy	

Continued

Table 2 Continued

COS	Papers containing an ADR in COS (/15)		Patients given LTRA in COS*	Patients suspected ADR in COS*	Characterised ADRs reported (/48)	Papers containing ADR (/15)	Patients given LTRA	Patients suspected ADR	ADR terms given in paper (/73)
	Papers containing an ADR in COS (/15)	Patients given LTRA in COS*							
Gastrointestinal disorders	7	2327	35	46	Abdominal pain	7	2327	19	Abdominal discomfort; abdominal pain; funny feeling in tummy; stomach ache
					Aphthous ulcers	1	1024	2	Aphthous ulcers
					Diarrhoea	1	312	1	Diarrhoea
					Nausea and vomiting symptoms	4	1196	13	Nausea; nausea or vomiting; vomiting
<b>Nervous system disorders</b>	7	2395	46	46	Dysesthesia	1	1	1	Dysesthesia
					Gait disturbance	1	1	1	Gait disturbance developed
					Headache	5	2373	21	Headache
					Nervous system disorders	1	21	7	Nervous system disorders
					Paraesthesia	1	1	2	Diminished sensation of pain and touch; numbness and pain of fingers
					Seizure	1	1024	2	Convulsion
					Somnolence	3	1442	12	Excessive sleepiness; drowsiness; drowsiness or lethargy
General disorders and administration site conditions	2	882	4	4	Fever	2	882	4	Fever
Metabolism and nutrition disorders	2	1074	9	9	Decreased appetite	1	50	8	Anorexia
					Increased appetite	1	1024	1	Increased appetite
Respiratory, thoracic and mediastinal disorders	2	882	2	2	Cough	1	881	1	Cough
					Sinusitis	1	1	1	Right paranasal sinusitis
Social circumstances	2	57	3	3	Educational problems	2	57	3	Decline in school performance
Cardiac disorders	1	312	1	1	Tachycardia	1	312	1	Tachycardia
Ear and labyrinth disorders	1	312	2	2	Dizziness or vertigo	1	312	2	Dizziness or vertigo
Hepatobiliary disorders	1	50	9	9	Abnormal liver function test	1	50	9	Abnormal liver function test
Immune system disorders	1	1	1	1	Rheumatoid factor quantitative increased	1	1	1	Higher rheumatoid factor

Continued

Table 2 Continued

COS	Papers containing an ADR in COS (/15)	Patients given LTRA in COS*	Patients with ADR in COS* suspected	Characterised ADRs reported (/48)	Papers containing ADR (/15)	Patients given LTRA	Patients with suspected ADR	ADR terms given in paper (73)	
								ADR	ADR
Musculoskeletal and connective tissue disorders	1	1	6	Arthritis	1	1	1	Arthritis	
				Arthralgia	1	1	1	Polyarthralgia	
				Churg-Strauss syndrome	1	1	1	Churg-Strauss syndrome	
				Muscle atrophy	1	1	1	Muscle atrophy	
				Muscle weakness in arm	1	1	1	Muscle weakness in arm	
				Myalgia	1	1	1	Myalgia	
Skin and subcutaneous tissue disorders	1	1024	3	Rash	1	1024	3	Rash	

Reported ADR data presented using Medical Dictionary for Regulatory Activities terminology and organised into COS. See method for ADR characterising process. ADR, adverse drug reaction; COS, Core Outcome Set; LTRA, leukotriene receptor antagonist.

## Statistical methods

Summary statistics were performed but meta-analysis was not conducted due to differences between studies.

## Patient and public involvement

This systematic review included substantial input from VS to provide patient representative, as a representative of an existing patient advocacy group. This was to ensure the scope of the review, the data presented and the conclusions reached were informed by patient perspectives.

## RESULTS

After duplicates were removed, the search identified 427 papers. We excluded 383 papers based on the title and abstract, and a further 29 following full-text screening. Fifteen papers met the eligibility criteria (figure 1 and table 1). Eligible papers comprised seven case reports, seven case-controlled or cohort studies and one RCT. Four out of the eight studies were prospective. In total, 7012 patients were recorded, of which 6853 received an LTRA. Thirteen papers examined the ADRs attributed to montelukast, one to pranlukast and one to unspecified LTRAs. Further characteristics of the studies are presented in table 1.

### Risk of bias or quality of data assessment of included studies

Online supplemental tables S2–S4 show the results of the risk of bias and quality of data assessments for the 15 papers examined. The RCT was judged to have low risk. Four of the five case-controlled or cohort studies also had low risk (good), with one having some risk (fair) due to the selection process used. Both non-comparative studies showed good quality of data but demonstrated some uncertainty during post-intervention data recording. Lastly, four of the seven case studies had low risk of bias, with the remaining three having an unclear risk of bias in three of the eight criteria domains.

### ADRs identified

A total of 73 different ADR terms were identified across the papers. Following language standardisation (online supplemental table S5), 48 distinct ADRs were identified and classified based on their class organ system (online supplemental table S6). The ADRs identified belonged to 13 different class organ systems.

Twenty of the 48 ADRs reported were classified as psychiatric disorders, the class organ system with the largest range of ADRs in this review. Additionally, ADRs in this class organ system appeared most frequently across the studies, with 10 of the 15 studies identifying at least one LTRA-induced psychiatric adverse event (table 2).

The most widely reported psychiatric disorders were ‘agitation/hyperactivity/nervousness/irritability’ (seven studies), ‘anxiety’ (six studies) and ‘sleep disorders’ (five studies). ADRs in the class organ systems of gastrointestinal disorders or nervous system disorders were the second most widely identified ADRs, appearing in 7 of

**Table 3** Estimated likelihood of ADR presentation reported in prospective studies and RCT

COS of ADR	Characterised ADR	Papers containing ADR (/4)	Patients with suspected ADR across prospective studies	Likelihood (%) of patient to experience an LTRA—induced ADR	SmPC frequency term
Psychiatric disorders	Agitation/hyperactivity/irritability/nervousness	1	24	2.3	Common
Psychiatric disorders	Aggression	1	11	1.0	Common
Nervous system disorders	Headache	2	11	1.0	Common
Hepatobiliary disorders	Abnormal liver function test	1	9	0.9	Uncommon
Metabolism and nutrition disorders	Decreased appetite	1	8	0.8	Uncommon
Nervous system disorders	Nervous system disorders	1	7	0.7	Uncommon
Psychiatric disorders	Sleep terror	1	7	0.7	Uncommon
Psychiatric disorders	Anxiety	1	7	0.7	Uncommon
Gastrointestinal disorders	Nausea and vomiting symptoms	1	5	0.5	Uncommon
General disorders and administration site conditions	Fever	1	3	0.3	Uncommon
Psychiatric disorders	Insomnia	1	3	0.3	Uncommon
Social circumstances	Decline in school performance	1	2	0.2	Uncommon
Gastrointestinal disorders	Abdominal pain	1	2	0.2	Uncommon
Respiratory, thoracic and mediastinal disorders	Cough	1	1	0.1	Uncommon

A total of 1050 patients administered an LTRA across the four prospective studies and RCT. See method for ADR characterising process.

ADR, adverse drug reaction; LTRA, leukotriene receptor antagonist; RCT, randomised control trial; SmPC, Summary of Product Characteristics.

the 15 studies each. The ADR of ‘abdominal pain’ was identified in all seven of the papers where a drug-induced gastrointestinal disorder was reported (table 2).

### Frequency of ADRs identified

The frequency of the identified ADR was also recorded, classified as the number of patients who experienced the ADR within the population where that ADR was identified. The number of ADR events per patient was unknown in all but one study so was not included in this analysis (table 2).<sup>26</sup>

Without accounting for population size, the most frequently reported ADRs were ‘anxiety’, ‘sleep disorders’ and ‘mood disorders’. Twenty of the 48 ADRs were only identified in a single patient across all studies (table 2).

The frequency data from the prospective studies and RCT, and case reports (table 4 and online supplemental table S7) were additionally examined separately.

### Attribution of frequency terms—prospective studies and RCT

Table 3 provides a breakdown of the frequencies of the ADRs by class organ system reported in the prospective

studies and RCT.<sup>26–29</sup> Following SmPC guidelines, a standardised frequency term was generated (very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1000$  to  $< 1/100$ ); rare ( $\geq 1/10\ 000$  to  $< 1/1000$ ); very rare ( $< 1/10\ 000$ )).<sup>25</sup> The total number of patients who were administered with an LTRA across the four prospective studies/RCT (1050 patients) was used as the denominator. Fourteen characterised ADRs were identified.

### Common

Three ADRs were identified as being ‘common’ ( $\geq 1/100$  to  $< 1/10$ ) as defined by SmPC documentation (table 3).<sup>25</sup> This included two ADRs within the class organ system of psychiatric disorders and one nervous system disorders. The nervous system disorder of ‘headache’ was identified in two of the four studies. The other two ‘common’ ADRs were ‘agitation/hyperactivity/irritability/nervousness’ and ‘aggression’ and were only identified in one of the four studies each.



**Table 4** The ADRs recorded per case study

Case study	Total ADRs reported	COS affected	ADR terms given in case report (/73)
Byrne, <i>et al</i>	3	2	Bruxism Funny feeling in his tummy Sleepwalking
Kobayashi, <i>et al</i>	12	4	Arthritis Churg-Strauss syndrome Diminished sensation of pain and touch Dysesthesia Gait disturbance developed Higher rheumatoid factor Muscle atrophy Muscle weakness in arm Myalgia Numbness and pain of fingers Polyarthralgia Right paranasal sinusitis
Kocigit, <i>et al</i>	3	1	Anxiety Hallucination Insomnia
Montoro De Francisco, <i>et al</i>	1	1	Fever
Scholz, <i>et al</i>	5	2	Decline in school performance Irritability Nervousness Reduced attention span Restlessness
Skillman, <i>et al</i> (1/2)	7	1	Crying when waking Disorientated when waking Irritable Night terrors Sleepwalking Separation anxiety Tantrums
Skillman, <i>et al</i> (2/2)	5	2	Anxiety Separation anxiety Difficulty falling asleep without parent Stomach pain Nausea
Star	10	2	Abdominal pain Anxiety Change in mood Change in sleeping patterns Depression Felt he was going crazy Nausea Sleeping badly Suicidal ideation Vomiting

The case reports identify eight patients who presented with a leukotriene receptor antagonist-induced ADR. The ADR terms as described in the case reports are given.

ADR, adverse drug reaction; COS, Core Outcome Set.

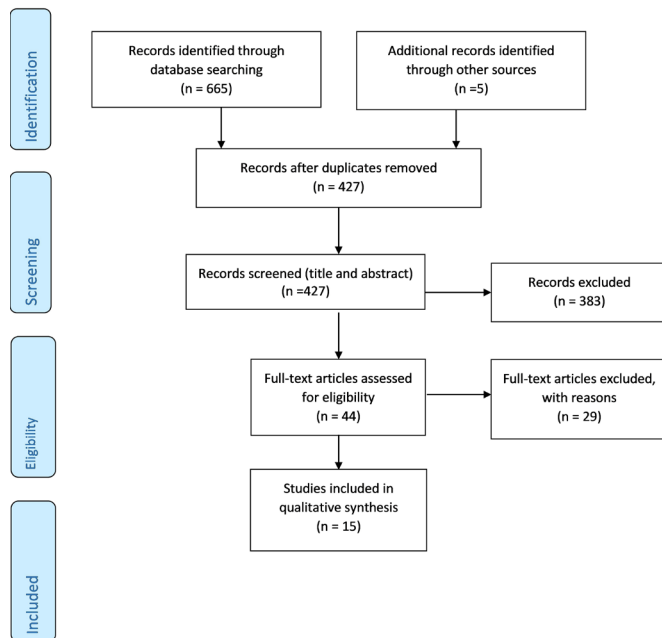
### Uncommon

Eleven ADRs were identified as being ‘uncommon’ ( $\geq 1/1000$  to  $< 1/100$ ) as defined by SmPC documentation (table 3).<sup>25</sup> Each ADR was only identified in one of the four prospective studies/RCT.

None of the ADRs identified across the prospective studies or RCT had a presentation likelihood frequency of rare ( $\geq 1/10\ 000$  to  $< 1/1000$ ) or very rare ( $< 1/10\ 000$ ).

### Case report data

Online supplemental table S7 depicts a breakdown of the frequencies of the ADRs by class organ system reported in the case reports. As the patients in the case reports were identified due to presenting an LTRA-induced ADR, a likelihood calculation was inappropriate. Thirty-seven different ADRs were identified across the seven case reports. Fifteen different ADRs were included in the class



**Figure 1** PRISMA flow diagram.

organ system of psychiatric disorders, the largest number of ADRs out of the eight identified class organ systems. Psychiatric disorders were found most commonly across the seven case reports with five of the seven reports identifying an ADR in this class organ system.

Forty-six different ADRs were experienced by a total of eight patients (table 4). All but one patient<sup>30</sup> presented with  $\leq 3$  different ADRs, with one patient presenting 12 different ADRs across four class organ systems.<sup>31</sup>

## DISCUSSION

Without accounting for the population size of the studies or trials, the most frequently reported ADRs across all studies were ‘anxiety’, ‘sleep disorders’ and ‘mood disorders’. With 15%–30% of 2–5 years old and 11%–15% of 6–12 years old have behavioural sleep problems, these ADRs can be challenging to diagnose, especially when LTRA can induce an ADR at any point after drug administration.<sup>32 33</sup> Clinical teams need to be aware of these ADRs as they are common in the child population and may alter the risk benefit profile of the drug.<sup>34</sup>

Montelukast is associated with a high frequency of neuropsychiatric ADR reports, including rare accounts of suicide,<sup>18</sup> but there are other systems, notably the gastrointestinal tract, where ADRs are also regularly reported. This is well aligned with the UK national spontaneous reporting (Yellow Card) data from the Medicines and Healthcare products Regulatory Agency.<sup>35</sup> Additionally, single large doses taken in error by CYP show predominantly gastrointestinal ADRs, with neuropsychiatric ADRs being less common.<sup>36</sup>

It is important not to view suspected ADRs in isolation, as LTRAs are an efficacious preventative treatment for asthma.<sup>6 7 37 38</sup> Many randomised double-blind

comparative studies have demonstrated montelukast’s anti-inflammatory mechanism of action; both its ability to cause significant reductions in peripheral blood eosinophils and fractional exhaled nitric oxide (demonstrative of reduced airway inflammation) in children have been widely documented.<sup>38–40</sup>

However, all new prescriptions and reviews of patients on existing medication should take account of the potential risks and benefits and evolving evidence in these areas. Recently, the FDA updated montelukast’s prescribing information document, acknowledging that the original clinical trials demonstrated that montelukast crosses the blood–brain barrier in substantial levels and not minimal levels as originally reported.<sup>32 41</sup> Further evidence of montelukast’s direct action on the brain was demonstrated in young murine models, where montelukast caused a decrease in the proliferation of neurons in the hippocampal region.<sup>42</sup> Importantly, the prescribing information document states that neuropsychiatric events have been also reported following montelukast discontinuation.<sup>32</sup> It is therefore a useful time to collate and review the known and suspected ADRs in children who use this medication to provide clinicians with the most up-to-date information.

Limitations of this review are primarily related to the way ADR data were presented, with only one clinical trial reporting the number of times that each ADR occurred in an individual and none reporting the time period over which the ADRs occurred.<sup>26</sup> Additionally, the proportion of patients who experienced multiple different ADRs is unknown, and it is not clear whether patients with multiple ADRs were within a single class organ system, or across a variety. This has prevented identification of any patterns of ADRs within or across systems and prevented the application of severity scores.

It is also possible that the review’s exclusion of studies where the ADRs presented were not significantly different from the placebo may have introduced bias through the potential exclusion of ADR data. However, false positives or ‘background noise’ are commonly reported in patients and healthy volunteers.<sup>43 44</sup> Studies examining ADR presentation should acknowledge the presence of false positives prior to the commencement of an ADR investigation.

At a population level, removing unnecessary step-up therapies such as montelukast when asthma is deemed ‘stable’ is encouraged by international guidelines.<sup>6 7</sup> However, the definition of ‘stable asthma’ is not clearly defined, and clinicians reviewing CYP with asthma who already using LTRAs will need to consider both the potential impact of stepping down therapy, as well the potential ADRs that may be occurring. We hope that this review will help structure the review of potential ADRs, helping to determine the appropriate treatment plan for an individual child.

## CONCLUSION

LTRAs have a wide range of suspected ADRs in children, predominantly neuropsychiatric and gastrointestinal. To

minimise the potential harms from ADRs, clinicians need to be aware of, and screen for, these ADRs. Careful monitoring of CYP with asthma is required, both to assess and manage ADRs and to step treatment down when clinically stable.

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# Adverse Drug Reactions of Leukotriene Receptor Antagonists in Children with Established Asthma: A Systematic Review (SUPPLEMENTARY DATA SECTION)

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Table S1: Search Strategy| The Healthcare Database Advanced Search Tool was used to conduct the literature search.

#	Database	Search term	Results
1	EMBASE	*JUVENILE/ OR *CHILD/ OR *BOY/ OR *GIRL/ OR *INFANT/ OR *TODDLER/ OR *"SCHOOL CHILD"/ OR *"PRESCHOOL CHILD"/	123145
2	EMBASE	*JUVENILE/ OR *ADOLESCENT/	41025
3	EMBASE	*ADOLESCENCE/ OR *PUBERTY/ OR *PUBESCENCE/ OR *PREPUBERTY/	23893
4	EMBASE	*PEDIATRICS/	39064
5	EMBASE	((Paediatric* OR Infan* OR Newborn* OR Bab* OR Neonat* OR Preterm* OR Prematur* OR Postmatur* OR Child* OR School* OR "Nursery school*" OR Kindergar* OR "Primary school*" OR "Secondary school*" OR "Elementary school*" OR "High school*" OR Highschool* OR Preschool* OR Kid* OR Toddler* OR Adoles* OR Teen* OR Boy* OR Girl* Minor* OR Pubert* OR Pubescen* OR Prepubescen*) NOT REVIEW*).ti,ab	3197725
6	EMBASE	(1 OR 2 OR 3 OR 4 OR 5)	3250524
7	EMBASE	6 [Humans]	2554004
8	EMBASE	*ASTHMA/ OR *"ASTHMA, BRONCHIAL"/	137351
9	EMBASE	((Asthma* OR Wheez* OR "Bronchial asthma*") NOT REVIEW).ti,ab	215606
10	EMBASE	(8 OR 9)	239908
11	EMBASE	10 [Humans]	197243
12	EMBASE	*"ADVERSE EVENT"/ OR *"ADVERSE DRUG REACTION"/ OR *"DRUG INDUCED DISEASE"/ OR *"UNSPECIFIED SIDE EFFECT"/ OR *"ADVERSE EFFECT"/ OR *"ADVERSE EFFECTS"/ OR *"ADVERSE EVENTS"/	153670
13	EMBASE	((adr* OR "adverse drug effect*" OR "adverse drug reaction*" OR "adverse effect*" OR "adverse event*" OR "adverse outcome*" OR "adverse reaction*" OR harm* OR risk* OR safe* OR "side effect*" OR tolerabilit* OR toxicit* OR treatment emergent* OR "undesirable effect*" OR "undesirable event*" OR "unexpected effect*" OR "unexpected event*" OR Complication*) NOT REVIEW).ti,ab	5660675
14	EMBASE	(12 OR 13)	5759103
15	EMBASE	14 [Humans]	4573760

16	EMBASE	*"LEUKOTRIENE RECEPTOR AFFECTING AGENT"/ OR *"LEUKOTRIENE RECEPTOR BLOCKING AGENT"/ OR *MONTELUKAST/ OR *PRANLUKAST/ OR *ZAFIRLUKAST/	4820
17	EMBASE	((LTRA OR "Leukotriene Receptor Antagonist*" OR Montelukast OR Singulair OR Pranlukast OR Onon OR Zafirlukast OR Accolate OR Idubilast OR Ketas OR Pinatos OR Eyevinal) NOT REVIEW).ti,ab	5682
18	EMBASE	(16 OR 17)	7511
19	EMBASE	18 [Humans]	5666
20	EMBASE	(6 AND 10 AND 14 AND 18)	434
21	EMBASE	20 [Humans]	412
22	Medline	*CHILD/ OR *"CHILD, PRESCHOOL"/	3959
23	Medline	*ADOLESCENT/ OR *MINORS/	6555
24	Medline	*INFANT/ OR *"INFANT, NEWBORN"/	18887
25	Medline	((Paediatric* OR Infan* OR Newborn* OR Bab* OR Neonat* OR Preterm* OR Prematur* OR Postmatur* OR Child* OR School* OR "Nursery school*" OR Kindergar* OR "Primary school*" OR "Secondary school*" OR "Elementary school*" OR "High school*" OR Highschool* OR Preschool* OR Kid* OR Toddler* OR Adoles* OR Teen* OR Boy* OR Girl* Minor* OR Pubert* OR Pubescen* OR Prepubescen* OR juvenile*) NOT REVIEW*).ti,ab	2759386
26	Medline	(22 OR 23 OR 24 OR 25)	2764845
27	Medline	*ASTHMA/	103573
28	Medline	((Asthma* OR Wheez* OR "Bronchial asthma*") NOT REVIEW).ti,ab	154652
29	Medline	(27 OR 28)	165873
30	Medline	*"DRUG-RELATED SIDE EFFECTS AND ADVERSE REACTIONS"/ OR *"METABOLIC SIDE EFFECTS OF DRUGS AND SUBSTANCES"/	19388
31	Medline	((adr* OR "adverse drug effect*" OR "adverse drug reaction*" OR "adverse effect*" OR "adverse event*" OR "adverse outcome*" OR "adverse reaction*" OR harm* OR risk* OR safe* OR "side effect*" OR tolerabilit* OR toxicit* OR treatment emergent* OR "undesirable effect*" OR "undesirable event*" OR "unexpected effect*" OR "unexpected event*" OR Complication*) NOT REVIEW).ti,ab	3948214

32	Medline	(30 OR 31)	3956208
33	Medline	*"LEUKOTRIENE ANTAGONISTS"/	1876
34	Medline	((LTRA OR "Leukotriene Receptor Antagonist*" OR Montelukast OR Singulair OR Pranlukast OR Onon OR Zafirlukast OR Accolate OR Idubilast OR Ketas OR Pinatos OR Eyevinal) NOT REVIEW).ti,ab	3503
35	Medline	(33 OR 34)	4184
36	Medline	(26 AND 29 AND 32 AND 35)	213
37	Medline	36 [Humans]	183
38	PubMed	((Paediatric* OR Infan* OR Newborn* OR Bab* OR Neonat* OR Preterm* OR Prematur* OR Postmatur* OR Child* OR School* OR "Nursery school*" OR Kindergar* OR "Primary school*" OR "Secondary school*" OR "Elementary school*" OR "High school*" OR Highschool* OR Preschool* OR Kid* OR Toddler* OR Adoles* OR Teen* OR Boy* OR Girl* Minor* OR Pubert* OR Pubescen* OR Prepubescen* OR juvenile*) NOT REVIEW*).ti,ab	224180
39	PubMed	((Asthma* OR Wheez* OR "Bronchial asthma*") NOT REVIEW).ti,ab	161313
40	PubMed	((adr* OR "adverse drug effect*" OR "adverse drug reaction*" OR "adverse effect*" OR "adverse event*" OR "adverse outcome*" OR "adverse reaction*" OR harm* OR risk* OR safe* OR "side effect*" OR tolerabilit* OR toxicit* OR treatment emergent* OR "undesirable effect*" OR "undesirable event*" OR "unexpected effect*" OR "unexpected event*" OR Complication*) NOT REVIEW).ti,ab	5478998
41	PubMed	((LTRA OR "Leukotriene Receptor Antagonist*" OR Montelukast OR Singulair OR Pranlukast OR Onon OR Zafirlukast OR Accolate OR Idubilast OR Ketas OR Pinatos OR Eyevinal) NOT REVIEW).ti,ab	3189
42	PubMed	(38 AND 39 AND 40 AND 41)	7
43	CINAHL	*CHILD/ OR *"CHILD, PRESCHOOL"/ OR *INFANT/ OR *ADOLESCENCE/ OR *"MINORS (LEGAL)"/	1676
44	CINAHL	*PEDIATRICS/ OR *NEONATOLOGY/	9355
45	CINAHL	((Paediatric* OR Infan* OR Newborn* OR Bab* OR Neonat* OR Preterm* OR Prematur* OR Postmatur* OR Child* OR School* OR "Nursery school*" OR Kindergar* OR "Primary school*" OR "Secondary school*" OR "Elementary school*" OR "High school*" OR Highschool* OR Preschool* OR Kid* OR Toddler* OR Adoles* OR Teen* OR Boy* OR Girl* Minor* OR Pubert* OR Pubescen* OR Prepubescen* OR juvenile*) NOT REVIEW*).ti,ab	841288



46	CINAHL	(43 OR 44 OR 45)	846753
47	CINAHL	*ASTHMA/	25840
48	CINAHL	((Asthma* OR Wheez* OR "Bronchial asthma*") NOT REVIEW).ti,ab	36444
49	CINAHL	(47 OR 48)	39664
50	CINAHL	*"ADVERSE DRUG EVENT"/	6520
51	CINAHL	((adr* OR "adverse drug effect*" OR "adverse drug reaction*" OR "adverse effect*" OR "adverse event*" OR "adverse outcome*" OR "adverse reaction*" OR harm* OR risk* OR safe* OR "side effect*" OR tolerabilit* OR toxicit* OR treatment emergent* OR "undesirable effect*" OR "undesirable event*" OR "unexpected effect*" OR "unexpected event*" OR Complication*) NOT REVIEW).ti,ab	1059456
52	CINAHL	(50 OR 51)	1061715
53	CINAHL	*"LEUKOTRIENE ANTAGONISTS"/ OR *MONTELUKAST/ OR *ZAFIRLUKAST/	570
54	CINAHL	((LTRA OR "Leukotriene Receptor Antagonist*" OR Montelukast OR Singulair OR Pranlukast OR Onon OR Zafirlukast OR Accolate OR Idubilast OR Ketas OR Pinatos OR Eyevinal) NOT REVIEW).ti,ab	764
55	CINAHL	(53 OR 54)	953
56	CINAHL	(46 AND 49 AND 52 AND 55)	63

## Results

Table S2: Results of assessment of risk bias of randomised control trials| The Cochrane Collaboration's tool was used. Green= low risk of bias, Yellow= unclear risk of bias, Red= high risk of bias.

	Lenny 2013
Random sequence generation (selection bias)	Green
Allocation concealment (selection bias)	Green
Binding of participants and personnel (performance bias)	Green
Binding of outcome assessment (detection bias)	Green
Incomplete outcome data (attrition Bias)	Green
Selective reporting (reporting bias)	Green
Other bias	Green

Table S3: Results of assessment of data quality of case-controlled and cohort studies| The Newcastle-Ottawa Quality Assessment Form was used. Green= star/ good quality, Yellow= unknown quality, Red= No star/ low quality.

	Ammar i 2018	Arnold 2020	Benard 2017	Erdem 2015	Glocker -Lauf 2018	Ghosh 2006	Kukreja 2004
Representativeness of the exposed cohort (selection bias)	Green	Green	Green	Green	Green	Green	Green
Selection of the non-exposed cohort (selection bias)	Red	Red	Green	Red	Red	Red	Red
Ascertainment of exposure (selection bias)	Green	Green	Green	Green	Green	Green	Green
Outcome of interest stated (selection bias)	Green	Green	Green	Green	Red	Green	Green
Comparability bias	Green	Green	Green	Green	Green	Red	Red
Assessment of outcome (outcome bias)	Green	Green	Green	Green	Green	Green	Green
Appropriate follow-up of outcomes (outcome bias)	Green	Green	Red	Green	Green	Green	Green
Appropriate follow-up of patients (outcome bias)	Green	Green	Green	Green	Green	Green	Green
<b>Overall quality</b>	Good	Good	Good	Good	Fair	Fair	Fair

Table S4: Results of assessment of risk bias of case studies| Murad MH, et al's tool was used. Green= low risk of bias, Yellow= unknown risk of bias, Red= high risk of bias.

	Byrne 2012	Kobayashi 2003	Kocyigit 2013	Montoro De Francisco 2015	Scholz 2019	Skillman 2011	Star 2011
Selection bias	Green	Green	Green	Green	Green	Green	Green
Exposure (ascertainment bias)	Green	Green	Green	Green	Green	Green	Green
Outcome (ascertainment bias)	Yellow	Green	Green	Green	Green	Green	Green
Observation (causality bias)	Green	Green	Green	Green	Green	Green	Green
Challenge/ rechallenge (causality bias)	Yellow	Yellow	Yellow	Green	Yellow	Yellow	Green
Dose-response effect (causality bias)	Yellow	Yellow	Yellow	Yellow	Yellow	Green	Green
Follow-up (causality bias)	Green	Green	Yellow	Green	Yellow	Green	Green
Reporting bias	Green	Green	Green	Green	Green	Green	Green

Table S5: Language Standardisation | The language used to describe the adverse drug reaction in the studies was standardised through MedDRA or medical terms. \* The adverse drug reaction term given in the study or MedDRA suggested synonyms for the term was not found in the MedDRA database and therefore a medical term was given to the reaction term by the same two consultant paediatricians based upon the age of the participants in the study and the consultants' experience in paediatric medicine.

Class Organ System	Terms Used in Study (n=73)	Preferred MedDRA (*Medical) Term
Psychiatric Disorders	Aggression	Aggression
	Agitation	Agitation
	Agitation/ hyperactivity	Agitation/ hyperactivity*
	Agitation/ irritability	Agitation/ irritability
	Anxiety	Anxiety
	Behaviour problems	Behaviour disorder
	Bruxism	Bruxism
	Change in mood	Mood disorders NEC
	Changes in sleeping patterns	Sleep disorders
	Crying when waking	Sleep terror*
	Depression	Depression
	Depressive state	Depression
	Difficulty falling asleep without parent	Sleep disorder NEC*
	Disorientated when walking	Disorientation
	Felt he was going crazy	Thinking abnormal*
	Hallucination	Hallucination
	Hyperactivity	Hyperactivity*
	Insomnia	Insomnia
	Irritability	Irritability
	Mood	Mood disorder NEC*
	Mood swings	Mood swings
	Nervousness	Nervousness
	Nervousness, agitation	Nervousness, agitation
	Nightmares	Nightmares
	Nyctophobia	Nyctophobia*
	Personality	Personality disorders NEC*
	Reduced attention span	Disturbance in attention*
	Restlessness	Restlessness
	Schizophrenia	Schizophrenia
	Separation anxiety	Separation anxiety disorder
	Sleep disorder, depression	Sleep disorder, depression
Sleep disturbance	Sleep disorder	
Sleeping badly	Sleep disorder	
Sleepwalking	Somnambulism	
Substance-related	Substance related and addictive disorders	
Suicidal ideation	Suicidal ideation	
Tantrums	Tantrums*	
Gastrointestinal Disorders	Abdominal discomfort	Abdominal discomfort
	Abdominal pain	Abdominal pain
	Aphthous ulcers	Aphthous ulcers*
	Diarrhea	Diarrhea

	Funny feeling in tummy	Abdominal discomfort
	Nausea	Nausea
	Nausea or vomiting	Nausea and vomiting symptoms
	Stomach aches	Abdominal pain upper
	Vomiting	Vomiting
<b>Nervous System Disorders</b>	Convulsion	Seizure
	Diminished sensation of pain and touch	Neurological disorders NOS*
	Drowsiness	Somnolence
	Drowsiness or lethargy	Somnolence or lethargy
	Dysesthesia	Dysesthesia
	Excessive sleepiness	Somnolence*
	Gait disturbance developed	Gait disturbance
	Headache	Headache
	Nervous system disorders	Nervous system disorders
Numbness and pain of fingers	Paraesthesia	
<b>General Disorders and Administration Site Conditions</b>	Fever	Pyrexia
<b>Metabolism and Nutrition Disorders</b>	Anorexia	Decreased appetite
	Increased appetite	Increased appetite
<b>Respiratory, Thoracic and Mediastinal Disorders</b>	Cough	Cough
	Right paranasal sinusitis	Sinusitis
<b>Social Circumstances</b>	Decline in school performance	Educational problems
<b>Cardiac Disorders</b>	Tachycardia	Tachycardia
<b>Ear and Labyrinth Disorders</b>	Dizziness or vertigo	Dizziness or vertigo
<b>Hepatobiliary Disorders</b>	Elevated liver function test	Abnormal liver function test*
<b>Immune System Disorders</b>	Higher rheumatoid factor	Rheumatoid factor quantitative increased
<b>Musculoskeletal and Connective Tissue Disorders</b>	Arthritis	Arthritis
	Muscle atrophy	Muscle atrophy
	Muscle weakness in arm	Muscle weakness in arm
	Myalgia	Myalgia
	Polyarthralgia	Arthralgia
	Churg-Strauss Syndrome	Churg-Strauss Syndrome*
<b>Skin and Subcutaneous Tissue Disorders</b>	Rash	Rash

Table S6: Adverse Drug Reaction Grouping | Similar adverse drug reactions were grouped together to facilitate data analysis.

Class Organ System	Terms Used in Study (n=73)	Terms used in Systematic Review (n=48)
<b>Psychiatric Disorders</b>	Aggression	Aggression
	Agitation Agitation/ hyperactivity Agitation/ irritability Hyperactivity Irritability Nervousness Nervousness/ agitation	Agitation/ hyperactivity/ irritability/ nervousness
	Anxiety Separation anxiety	Anxiety
	Behaviour problems Tantrums	Behaviour disorders
	Bruxism	Bruxism
	Depression Depressive state	Depression
	Disorientated when waking	Disorientation
	Reduced attention span	Disturbance in attention
	Hallucination	Hallucination
	Insomnia	Insomnia
	Change in mood Mood Mood swings Personality	Mood disorders
	Nyctophobia	Nyctophobia
	Restlessness	Restlessness
	Schizophrenia	Schizophrenia
	Substance-related	Substance related and addictive disorders
	Change in sleeping patterns Difficulty falling asleep without parent Sleep disorder/ depression Sleep disturbance Sleeping badly	Sleep disorders
	Crying when waking Nightmares	Sleep terror
	Sleepwalking	Somnambulism
	Suicidal ideation	Suicidal ideation
	Felt he was going crazy	Thinking abnormal
<b>Gastrointestinal Disorders</b>	Abdominal discomfort Abdominal pain Funny feeling in tummy Stomachache	Abdominal pain
	Apthous ulcers	Apthous ulcers
	Diarrhea	Diarrhea

	Nausea Nausea or vomiting Vomiting	Nausea and vomiting symptoms
<b>Nervous System Disorders</b>	Dysesthesia	Dysesthesia
	Gait disturbance developed	Gait disturbance
	Headache	Headache
	Nervous system disorders	Nervous system disorders
	Diminished sensation of pain and touch Numbness and pain of fingers	Paraesthesia
	Convulsion	Seizure
	Excessive sleepiness Drowsiness Drowsiness or lethargy	Somnolence
<b>General Disorders and Administration Site Conditions</b>	Fever	Pyrexia
<b>Metabolism and Nutrition Disorders</b>	Anorexia	Decreased appetite
	Increased appetite	Increased appetite
<b>Respiratory, Thoracic and Mediastinal Disorders</b>	Cough	Cough
	Right paranasal sinusitis	Sinusitis
<b>Social Circumstances</b>	Decline in school performance	Educational problems
<b>Cardiac Disorders</b>	Tachycardia	Tachycardia
<b>Ear and Labyrinth Disorders</b>	Dizziness or vertigo	Dizziness or vertigo
<b>Hepatobiliary Disorders</b>	Elevated liver function test	Abnormal liver function test
<b>Immune System Disorders</b>	Higher rheumatoid factor	Rheumatoid factor quantitative increased
<b>Musculoskeletal and Connective Tissue Disorders</b>	Arthritis	Arthritis
	Polyarthralgia	Arthralgia
	Churg-Strauss Syndrome	Churg-Strauss Syndrome
	Muscle atrophy	Muscle atrophy
	Muscle weakness in arm	Muscle weakness in arm
<b>Skin and Subcutaneous Tissue Disorders</b>	Myalgia	Myalgia
	Rash	Rash

Table S7: ADRs reported in Case Reports| The recorded frequencies of ADRs per class organ system.

<b>Class Organ System of ADR</b>	<b>Papers Containing an ADR (/7) (n)</b>	<b>Types of ADRs Reported (/48) (n)</b>	<b>Patients Given LTRA (/7) (n)</b>	<b>Total ADRs Reported (n)</b>
Psychiatric Disorders	5	15	6	26
Gastrointestinal Disorders	3	2	4	6
General Disorders and Administration Site Conditions	1	1	1	1
Immune System Disorders	1	1	1	1
Musculoskeletal and Connective Tissue Disorders (MC)	1	6	1	6
Nervous System Disorders	1	3	1	4
Respiratory, Thoracic and Mediastinal Disorders	1	1	1	1
Social Circumstances	1	1	1	1