BMJ Paediatrics Open

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

Eleanor Grace Dixon 1,2, Charlotte EM Rugg-Gunn 1,2,3 Vanessa Sellick,4 Ian P Sinha,2,5 Daniel B Hawcutt2,6

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’, ‘agression’ 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.

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.

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.1,2 The UK has the highest prevalence of childhood asthma symptoms in the world, with the National Health Service spending around 1 billion pounds each year on asthma care.3 4 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.5–7

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.8–10 Montelukast, the originator drug in this class, has also been separately licenced for allergic rhinitis in some nations.11–13 Initially licenced in 1998, montelukast was the 16th most prescribed medication in 2020 globally.12,13

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)’.14 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. There was particular concern regarding significant neuropsychiatric events associated with this drug. These included suicidal thoughts and actions, depression and sleeping problems.

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.

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 (1/15), cohort or case-control studies (7/15) and case studies (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 in the references. 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.

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.
| First author  | Year | Type of study                                                                 | Patients (of relevant age) | Patients administered the LTRA | Age of patients | Participant characteristics (as presented in study) | Leukotriene receptor antagonist | LTRA administered | Dose information given | Length of drug administration prior to ADR presentation | Other drugs administered by patients |
|--------------|------|--------------------------------------------------------------------------------|---------------------------|-------------------------------|----------------|---------------------------------------------------|-----------------------------|-------------------|----------------------------|-----------------------------------------------------|-----------------------------------------|
| Lenney       | 2013 | Randomised, double-blind, placebo controlled, parallel study                  | 63                        | 21                            | 6–14 years                           | 40 males, 23 females (whole study)                     | Montelukast                 | 5 mg/day             | 0–48 weeks                               | Inhaled fluticasone propionate 100 µg two times per day. |
| Ammari       | 2018 | Prospective cohort study                                                      | 56                        | 56                            | 2–17 years                           | Not specified                                         | Montelukast                 | Not specified        | 1–24 weeks                               | Inhaled steroids.                           |
| Ghosh        | 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. |
| Kukreja      | 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’. |
| Arnold       | 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.                           |
| Benard       | 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.                           |
| Erdem        | 2015 | Retrospective cohort study                                                    | 1024                      | 1024                          | Not specified ('children')           | Not specified                                         | Not specified               | Not specified        | Not specified | Not specified.                           |
| Glocker-Lauf | 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. |
| Kobayashi    | 2003 | Case report                                                                    | 1                         | 1                             | 17 years                             | Japanese male                                         | Pranlukast                  | 450 mg/day           | 13 months                               | Theophylline 400 mg/day.                   |
| Kocyigit     | 2013 | Case report                                                                    | 1                         | 1                             | 13 years                             | Male                                                  | Montelukast                 | Not specified        | 24–36 hours                             | Salbutamol, formoterol and budesonide.     |

Continued
| First author       | Year | Type of study | Patients (of relevant age) | Patients administered the LTRA | Age of patients | Participant characteristics (as presented in study) | Leukotriene receptor antagonist | Dose information given | Length of drug administration prior to ADR presentation | Additional drugs administered by patients |
|-------------------|------|---------------|---------------------------|-------------------------------|----------------|--------------------------------------------------------|---------------------------------|------------------------|-----------------------------------------------------|----------------------------------------------|
| Byrne             | 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. |
| Montoro De Francisco | 2015 | Case report   | 1                         | 1                             | 7 years        | Male                                                   | Montelukast                     | 4 mg/day               | 12 hours                                           | Not specified. |
| Scholz            | 2019 | Case report   | 1                         | 1                             | 11 years       | Male                                                   | Montelukast                     | Not specified          | 4 months                                           | Salbutamol and salmeterol/fluticasone. |
| Skillman          | 2011 | Case report   | 2                         | 2                             | 1. 4 years     | 1. Male                                                | Montelukast                     | 1. 5 mg/day            | 1. Since starting since does increase after child's sixth birthday | 1. Albuterol 2.5 mg nebulised every 4–6 hours, cetirizine 5 mg daily. |
|                   |      |               |                           |                               | 2. 6 years     | 2. Hispanic female                                     |                                 | 2. 4 mg/day then 5 mg/day | 2. Fluticasone oral inhaler 44 mcg two times per day, cetirizine 5 mg.   |  |
| Star              | 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 given LTRA in COS (7/15) | Patients with suspected ADR in COS* (7/15) | Characterised ADRs reported (/48) | Papers containing ADR (/15) | Patients given LTRA | Patients with suspected ADR | ADR terms given in paper (73) |
|--------------------------|----------------------------------------|------------------------------------|---------------------------------------------|---------------------------------|---------------------------|---------------------|-----------------------------|--------------------------------|
| Psychiatric disorders    | 10                                     | 5899                               | 1100                                        | Aggression                      | 2                         | 162                 | 18                          | Aggression; agitation/hyperactivity; agitation/irritability; hyperactivity; irritability; nervousness; nervousness/agitation |
|                          |                                        |                                    |                                             | Agitation/ hyperactivity/ irritability/nervousness | 7                         | 5899                 | 64                          |                                |
|                          |                                        |                                    |                                             | 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
| COS                                           | Papers containing an ADR in COS (/15) | Patients given LTRA in COS* | Patients with suspected ADR in COS* | Characterised ADRs reported (/48) | Papers containing ADR (/15) | Patients given LTRA | Patients with suspected ADR | ADR terms given in paper (/73)                                                                 |
|-----------------------------------------------|--------------------------------------|-----------------------------|-------------------------------------|----------------------------------|----------------------------|----------------------|--------------------------|---------------------------------------------------------------------------------------------|
| Gastrointestinal disorders                    | 7                                    | 2327                        | 35                                  | 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                                               |
| Nervous system disorders                      | 7                                    | 2395                        | 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                                   | Fever                            | 2                          | 882                   | 4                       | Fever                                                                     |
| Metabolism and nutrition disorders            | 2                                    | 1074                        | 9                                   | Decreased appetite               | 1                          | 50                    | 8                       | Anorexia                                                                  |
|                                               |                                       |                             |                                     | Increased appetite               | 1                          | 1024                  | 1                       | Increased appetite                                                        |
| Respiratory, thoracic and mediastinal disorders | 2                                    | 882                         | 2                                   | Cough                            | 1                          | 881                   | 1                       | Cough                                                                     |
|                                               |                                       |                             |                                     | Sinusitis                        | 1                          | 1                     | 1                       | Right paranasal sinusitis                                                    |
| Social circumstances                          | 2                                    | 57                          | 3                                   | Educational problems             | 2                          | 57                    | 3                       | Decline in school performance                                                |
| Cardiac disorders                             | 1                                    | 312                         | 1                                   | Tachycardia                      | 1                          | 312                   | 1                       | Tachycardia                                                              |
| Ear and labyrinth disorders                   | 1                                    | 312                         | 2                                   | Dizziness or vertigo              | 1                          | 312                   | 2                       | Dizziness or vertigo                                                       |
| Hepatobiliary disorders                       | 1                                    | 50                          | 9                                   | Abnormal liver function test      | 1                          | 50                    | 9                       | Abnormal liver function test                                                  |
| Immune system disorders                       | 1                                    | 1                           | 1                                   | Rheumatoid factor quantitative increased | 1                      | 1                     | 1                       | Higher rheumatoid factor                                                     |

Table 2 Continued
### 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. Fourteen papers met the eligibility criteria (figure 1). Thirteen papers were included and presented in the table.

#### ADRs identified

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

### ADRs in COS

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

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.
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).26

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.26–29 Following SmPC guidelines, a standardised frequency term was generated (very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10 000 to <1/1000); very rare (<1/10 000)). 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.

| COS of ADR                  | Characterised ADR                                      | 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              |
| Gastrointestinal disorders   | Abdominal pain                                         | 1                                                      | 9                                                          | 0.9                 | Uncommon            |
| Nervous system disorders     | Agitation/hyperactivity/irritability/nervousness       | 1                                                      | 8                                                          | 0.8                 | Uncommon            |
| Metabolism and nutrition disorders | Decreased appetite                              | 1                                                      | 8                                                          | 0.8                 | Uncommon            |
| Hepatobiliary disorders      | Abnormal liver function test                          | 1                                                      | 9                                                          | 0.9                 | 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            |

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

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.
Uncommon

Eleven ADRs were identified as being ‘uncommon’ (≥1/1000 to <1/100) as defined by SmPC documentation (Table 3). 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 (≥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

---

Table 4 The ADRs recorded per case study

| Case study            | Total ADRs reported | COS affected | ADR terms given in case report (/73)                                                                 |
|-----------------------|---------------------|--------------|------------------------------------------------------------------------------------------------------|
| Byrne, et al          | 3                   | 2            | Bruxism  
 Funny feeling in his tummy  
 Sleepwalking |
| Kobayashi, et al      | 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 |
| Kocyigit, et al       | 3                   | 1            | Anxiety  
 Hallucination  
 Insomnia |
| Montoro De Francisco, et al | 1 | 1 | Fever |
| Schoiz, et al         | 5                   | 2            | Decline in school performance  
 Irritability  
 Nervousness  
 Reduced attention span  
 Restlessness |
| Skillman, et al (1/2) | 7                   | 1            | Crying when waking  
 Disorientated when waking  
 Irritable  
 Night terrors  
 Sleepwalking  
 Separation anxiety  
 Tantrums |
| Skillman, et al (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.
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 identify 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 presented with ≤3 different ADRs, with one patient presenting 12 different ADRs across four class organ systems.31

**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.32–33 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.34

Montelukast is associated with a high frequency of neuropsychiatric ADR reports, including rare accounts of suicide,35 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.35 Additionally, single large doses taken in error by CYP show predominantly gastrointestinal ADRs, with neuropsychiatric ADRs being less common.36

It is important not to view suspected ADRs in isolation, as LTRAs are an efficacious preventative treatment for asthma.6,7,37,38 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.38–40

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.32,41 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.42 Importantly, the prescribing information document states that neuropsychiatric events have been also reported following montelukast discontinuation.33 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.26 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.33,44 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.6,7 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 GAP with asthma is required, both to assess and manage ADRs and to step treatment down when clinically stable.

Twitter Daniel B Hawcutt @pharmaford

Acknowledgements This is a summary of independent research carried out at the National Institute for Health Research (NIHR) Alder Hey Clinical Research Facility. The views expressed are those of the author(s) and not necessarily those of the National Health Service, the NIHR or the Department of Health.

Contributors EGD conducted the systematic review. This included establishing the eligibility criteria, conducting the search, collecting the data and analysing the results. CEMR-G conducted the data search in parallel and compared eligible papers with EGD. VS advised and provided information on known leukotriene receptor antagonist (LTRA)–induced adverse drug reaction (ADR) cases and LTRA policy. IS and DBH equally oversaw the direction of the review including editing the writing of the paper, acted as consultants in characterising ADRs and ensured clinical relevance to the review.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Disclaimer This is a summary of independent research carried out at the National Institute for Health Research (NIHR), Alder Hey Clinical Research Facility. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Competing interests VS has close relationships with individuals and families who identify as being adversely affected by montelukast side effects.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. Available from corresponding author on request.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution 4.0 (CC BY 4.0) license, which permits others to copy, redistribute, remix, transform and build upon this work for any purpose, provided the original work is properly cited, a link to the licence is given, and indication of whether changes were made. See: https://creativecommons.org/licenses/by/4.0/

ORCID iDs
Eleanor Grace Dixon http://orcid.org/0000-0001-9697-0068
Charlotte EM Rugg-Gunn http://orcid.org/0000-0003-1989-3489

REFERENCES
1 Ferrante G, La Grutta S. The burden of pediatric asthma. Front Pediatr 2018;6:186.
2 World Health Organisation. Asthma: World health organisation. 2020. Available: https://www.who.int/news-room/q-a-detail/asthma [Accessed 09 Sep 2020].
3 Asthma UK. Asthma deaths in the UK, 2001-2016, 2021. Available: https://www.asthma.org.uk/support-us/campaigns/data-visualisations/#Deaths [Accessed 29 Jan 2021].
4 Pharmaceutical Services Negotiating Committee. Essential facts, STAs and Quotes relating to asthma, 2020. Available: https://psnc.org.uk/services-commissioning/essential-facts-stats-and-quotes-relating-to-asthma/#:~:text=In%202014%20the%20most%20recent,every%2020classroom%20in%20the%20UK [Accessed 18 Nov 20].
5 Lundbäck B, Gibson J, Robert Loddenkemper YS, Gibson J, Lundbäck B, eds. Respiratory health and disease in Europe. In, 2013.
6 British Thoracic Society and the Scottish Intercollegiate Guidelines Network. SIGN158 British guidelines on the management of asthma. In: MRS Sheila Edwards, ED, 2019. Available: https://www.brit-thoracic.org.uk/quality-improvement/guidelines/asthma/.
7 Global Initiative for Asthma. Global strategy for asthma management and prevention, 2021. Available: https://ginasthma.org/wp-content/uploads/2021/04/GINA-2021-Main-Report_FINAL_21_04_28-WMS.pdf [Accessed 05 May 2021].
8 Tamada T, Ihojisse M. Leukotriene receptor antagonists and antihypertensives. HANDS EXP Pharm 2017;237:153-69.
9 U.S. Food and Drug Administration. Singular (montelukast) and All Montelukast Generics: Strengthened Boxed Warning - Due to Restricting Use for Allergic Rhinitis. 2020. Available: https://www.fda.gov/safety/medical-product-safety-information/singularmontelukast-and-all-montelukast-generics-strengthened-boxed-warning-due-restricting-use [Accessed 24 Mar 2021].
10 NPS Medicinewise. Consumer medicine information: Singular [9124] 2019, 2021. Available: https://www.nps.org.au/medicine-finder/ singular-tablets [Accessed 24 Mar 2021].
11 Lipworth BJ. Leukotriene-Receptor antagonists. Lancet. 1999;353:57–62.
12 Drugbank. Montelukast, 2020. Available: https://go.drugbank.com/ drugs/DB00471 [Accessed 09 Sep 2020].
13 OpenPrescribing. Montelukast (0303020G0), 2020. Available: https://openprescribing.net/chemical/0303020G0 [Accessed 14 Sep 2020].
14 National Institute for Health and Care Excellence. Adverse drug reactions [17/03/2017], 2017. Available: https://cks.nice.org.uk/topics/adverse-drug-reactions/ [Accessed 10 Sep 2020].
15 U.S. Food and Drug Administration. FDA requires stronger warning about risk of neuropsychiatric events associated with asthma and allergy medication Singular and generic montelukast, 2020.
16 Health Sciences Authority. Advisory on restriction on the use of montelukast and neuropsychiatric effects, 2021. Available: https://www.hsa.gov.sg/press-releases/safety-alert/advisory-on-restriction-on-the-use-of-montelukast-and-neuropsychiatric-effects [Accessed 24 Mar 2021].
17 National Agency for the Safety of Medicines and Health Products. Montelukast (Singulair et génériques) : risque de survenue d’effets indésirables neuropsychiatriques, renforcement des mises en garde, 2020. Available: https://ansm.sante.fr/informations-de-securite/ montelukast-singulair-et-genieres-risque-de-survenue-deffets-idesirables-neuropsychiatriques-renforcement-des-mises-en-garde [Accessed 24 Mar 2021].
18 Medicines and HealthCare Products Regulatory Agency. Fatal cases of adverse drug reactions in patients aged 0-19 years old attributed to montelukast. In: hedixon@livpooler.ac.uk (Recipient) yellow.card@mhra.gov.uk (Sender), ed 2020.
19 de Benedictis FM, Carloni I, Guidi R. Safety of anti-inflammatory drugs in children with asthma. Curr Opin Allergy Clin Immunol 2021;21:144–50.
20 Loke YK, Price D, Herxheimer A, et al. Systematic reviews of adverse effects: framework for a structured approach. BMC Med Res Methodol 2007;7:32.
21 Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane collaboration’s tool for assessing risk of bias in randomised trials. BMJ 2011:343:d5928.
22 Wells G, Shea B, O’Connell D. The Newcastle-Ortawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses: the Ottawa Hospital research Institute, 2019. Available: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp [Accessed 08 Dec 2020].
23 Murad MH, Sultan S, Halaf S, et al. Methodological quality and synthesis of case series and case reports. BMJ Evid Based Med 2018;23:60–3.
24 Medical Directory for Regulatory Activities. Medical dictionary for regulatory activities terminology (MedDRA), 2020. Available: http://biportal.bioontology.org/ontologies/MEDDRA2020 [Accessed 15 Oct 2020].
25 European Commission. A GUIDELINE ON SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) September 2009. In: Consumer goods: pharmaceuticals. European Commission, 2009: 16.
26 Lenney W, McKay AJ, Tudur Smith C, et al. Management of asthma in school age children (MASCOT): a randomised, double-blind, placebo-controlled, parallel study of efficacy and safety. Health Technol Assess 2013;17:1–218.
27 Ghosh G, Manglik AK, Roy S. Efficacy and safety of montelukast as monotherapy in children with mild persistent asthma. *Indian Pediatr* 2006;43:780–5.
28 Kukreja S, Sanjay S, Ghosh G, et al. Montelukast - evaluation in 6 to 14 years old children with persistent asthma - pediatric montelukast study group. *Indian J Pediatr* 2004;71:811–5.
29 Ammari S, Berraies A, Hamdi B. Montelukast: neuropsychiatric adverse drug reactions in Tunisian asthmatic children. *European Respiratory Journal* 2018;52:PA4610.
30 Montoro de Francisco A, Garcia Luque A, Tabakov A. 1268 fever associated with montelukast: a pediatric case. poster session group III – green TPS 39, *Allergy* 2015;70:527–613.
31 Kobayashi S, Ishizuka S, Tamura N, et al. Churg-Strauss syndrome (CSS) in a patient receiving pranlukast. *Clin Rheumatol* 2003;22:10.1007/s10067-003-0791-5.
32 U.S. Food and Drug Administration. Full prescribing information, 2021. Available: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/020829s074,020830s076,021409s052bl.pdf?bcid=lwa90p11a4y1n9g7e0opypn7n8dp3upox8heyece5fknr7pZ7-g94P5j [Accessed 24 Mar 2021].
33 Turnbull K, Reid GJ, Morton JB. Behavioral sleep problems and their potential impact on developing executive function in children. *Sleep* 2013;36:1077–84.
34 Electronic Medicines Compendium. Montelukast 5mg Chewable tablets, 2011. Available: https://www.medicines.org.uk/emc/product/6097/smpc#gref [Accessed 09 Dec 2020].
35 Medicines and Healthcare Products Regulatory Agency. Interactive drug analysis profile: montelukast, 2020. Available: https://info.mhra.gov.uk/drug-analysis-profiles/dap.html?drug= /UK_EXTERNAL/ NONCOMBINED/UK_NON_000897510683.zip&agency=MHRA [Accessed 03 Mar 2021].
36 Arnold DH, Bowman N, Reiss TF, et al. Adverse events are rare after single-dose montelukast exposures in children. *Clin Toxicol* 2019;57:25–18.
37 Batchelor HK, Marriott JF. Formulations for children: problems and solutions. *Br J Clin Pharmacol* 2015;79:405–18.
38 Harmanci K. Montelukast: its role in the treatment of childhood asthma. *Ther Clin Risk Manag* 2007;3:685–92.
39 Bisgaard H, Zielien S, Garcia-Garcia ML, et al. Montelukast reduces asthma exacerbations in 2- to 5-year-old children with intermittent asthma. *Am J Respir Crit Care Med* 2005;171:10.1164/rcrm.200407-894OC.3:15–22.
40 Bisgaard H, Loland L, OJJA. No in exhaled air of asthmatic children is reduced by the leukotriene receptor antagonist montelukast. *Am J Respir Crit Care Med* 1999;160:1227–31.
41 U.S. Food and Drug Administration. Meeting of the pediatric and drug safety and risk management committees, 2019. Available: https://www.fda.gov/media/132468/download [Accessed 29 Mar 2021].
42 Eriksson Y, Bostrom M, Sandelius Asa, et al. The anti-asthmatic drug, montelukast, modifies the neurogenic potential in the young healthy and irradiated brain. *Cell Death Dis* 2018;9:775.
43 Khosla PP, Bajaj VK, Sharma G, et al. Background noise in healthy volunteers--a consideration in adverse drug reaction studies. *Indian J Physiol Pharmacol* 1992;36:259–59.
44 Grundmark B, Holmberg L, Garmo H, et al. Reducing the noise in signal detection of adverse drug reactions by standardizing the background: a pilot study on analyses of proportional reporting ratios-by-therapeutic area. *Eur J Clin Pharmacol* 2014;70:627–35.
45 Arnold DH, Bowman N, Reiss TF, et al. Adverse events associated with weight-based, high-dose montelukast exposures in children. *Clin Toxicol* 2020;58:145–6.
46 Benard B, Bastien V, Vinet B, et al. Neuropsychiatric adverse drug reactions in children initiated on montelukast in real-life practice. *Eur Respir J* 2017;50:1700148.
47 Erdem SB, Nacaroglu HT, Unsal Karkiner CS, et al. Side effects of leukotriene receptor antagonists in asthmatic children. *Iran J Pediatr* 2015;25:e3313.
48 Glockler-Lauf SD, Finkelstein Y, Zhu J, et al. Montelukast and neuropsychiatric events in children with asthma: a nested case-control study. *J Pediatr* 2019;209:176–82.
49 Kocyigit A, Gulcan Oksuz B, Yarar F, et al. Hallucination development with montelukast in a child with asthma: case presentation. *Iran J Allergy Asthma Immunol* 2013;12:397–9.
50 Byrne F, Oluwole B, Whyte V, et al. Delayed onset of neuropsychiatric effects associated with montelukast. *Ir J Psychol Med* 2012;29:125–7.
51 Scholz I, Banholzer S, Haschke M. P90 Neuropsychiatric disorder and Montelukast: a case report and VigiBase® analysis. *Arch Dis Child* 2019;104:e54.2–5.
52 Skillman KL, Stumpf JL. Montelukast-induced anxiety in two pediatric patients. *Pharmacotherapy* 2011;31:524–24.
53 Star K. Detecting unexpected adverse drug reactions in children. *Paediatr Drugs* 2011;13:71–3.