PEER REVIEW HISTORY

BMJ Paediatrics Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Adverse Drug Reactions of Leukotriene Receptor Antagonists in Children with Asthma: A Systematic Review
AUTHORS	Dixon, Eleanor Rugg-Gunn, Charlotte Sellick, Vanessa Sinha, Ian Hawcutt, Daniel B

VERSION 1 – REVIEW

REVIEWER	Reviewer name: Dr. Claire Lefebvre Institution and Country: not applicable Competing interests: None
REVIEW RETURNED	26-Jul-2021

GENERAL COMMENTS	I thank the authors for the opportunity to review this manuscript. The question of adverse drug reactions in children is of great importance and more studies on this topic are needed. This is a systematic review of 7 case studies, 5 case-control or cohort studies, 2 non-comparative studies and one RCT with the objective of identifying and understanding the reported frequency of ADRs to leukotriene receptor antagonists in children and youth. This paper has a lot of interesting material and a collation of the published ADR reports for LTRA is important. However, my main issue with this paper is in the methodology. Specifically, I take issue with the denominator used for the ADR frequency calculations. I have several other comments listed below: Major methodology issue: The authors are reporting on frequency of ADRs across the 7 studies that have a denominator that allows this calculation. The denominator must therefore include the total number of participants prescribed a LTRA across all 7 studies examined – and NOT, as seems to be the case, only the number of participants who received the LTRA in ONLY the study that reported the ADR in question. For example, it appears that some ADRs were classified as very common simply because they only appeared in small studies (e.g. in 1 participant, in 1 study with fewer than 50 total participants). If this is the case, it is misleading and ignores all the other participants who took a LTRA and did NOT experience this ADR. Inclusion criteria issues: On page 6, Line 43 states that authors excluded studies that "stated that the ADRs presented were not significantly different from placebo". This can only apply to RCTs with a placebo group. Therefore, this exclusion criteria can only be applied to specific type of study and will not affect the inclusion of other types of studies – however low their ADR frequency might be. This therefore introduces bias by potentially excluding large RCTs with valuable data. I would argue that all studies reporting ADRs, regardless of frequency compared to placebo be included.

	On page 7, line 34, authors state that "when studies were reported in multiple publications, information was collected across these to maximize information available". Could the authors please clarify what is meant by this? How did the authors avoid ADRs being double counted if the study was reported in more than one publication? Clarification of methodology: On page 8, line 46, authors mention using MedDRA terminology and SmPCs guidelines – it would be helpful to briefly define these acronyms and explain the classification system. This would also help to clarify what the authors mean on page 11, line 59 "following SmPC guidelines, a standardized frequency term was generated" It is also unclear to me whether the classification of "very common vs. common vs. uncommon" refers to the frequency noted in the summary of product characteristics or the frequency noted in the present study. It would be very helpful for the authors to better describe the SmPC classification to which they refer. For example, they list several ADRs as being "very common" (e.g. nervous system disorders, elevated liver function tests, decreased appetite and aggression) but go onto say that most of these were only noted in 1 patient among fewer than 50. What is the cutoff for "very common"? Distinction between study types: I also think there should be a clearer distinction between the cohort/case-control/RCT studies and the case reports/case series which are methodologically extremely different. I would like to see the case reports discussed completely separately from the other studies. For example, eligibility criteria states that studies were included if they mentioned the frequency of ADRs. However, this cannot be determined for a case report. Therefore, inclusion criteria are inherently different depending on the type of study. Other: Also, please clarify what a non-comparative study. I do not believe this is a recognized study design. Please define the CYP acronym the first time it appears in the manuscript.

REVIEWER	Reviewer name: Dr. Fernando de Benedictis Institution and Country: Via Trilussa 87, Pescara, 65122, Italy Competing interests: None
REVIEW RETURNED	09-Aug-2021

GENERAL COMMENTS	Adverse Drug Reactions of Leukotriene Receptor Antagonists in Children with Asthma: A Systematic Review General comment This article aims to review the reported frequency of adverse drug reactions attributed to LTRAs in children with asthma. The authors should be congratulated for identifying this important aspect of paediatric pulmonology and undertaking this work. The study protocol is clear and well designed, the method used is excellent, and the results are well presented. The conclusions are acceptable. The tables are fine. The references are updated. At view, the general presentation of the article is very good. Minor comments The following comments may improve the text: - Abstract: The sentence "The aim was to…" should be moved to the

	Background section, so that the Method could be described in this specific section. - pag. 6, line 36: "for a diagnosis of asthma" - modify to "for asthma" - pag. 7, line 46: SmPC – spelling the acronymous at the first description - pag. 12, line 9: "elevated" – abnormal? - pag 12, line 9: "nervous system disorders" – add also psychiatric? Indeed, in the Table 3, 2nd column, Characterized ADR are not described. - I would suggest adding the following recent reference: 'de Benedictis et al., Safety of antinflammatory drugs in children with asthma, Curr Opin Allergy Immunol 2021', which adds something for ADRs of LTRAs.

VERSION 1 – AUTHOR RESPONSE

Dear Dr. Brodlie,

Thank you very much for reading my paper.

I have responded to your suggestions and uploaded my edited paper.

Kind regards,
Eleanor Dixon

VERSION 2 – REVIEW

REVIEWER	Reviewer name: Dr. Fernando de Benedictis Institution and Country: Via Trilussa 87, Pescara, 65122, Italy Competing interests: None
REVIEW RETURNED	09-Aug-2021

GENERAL COMMENTS	Adverse Drug Reactions of Leukotriene Receptor Antagonists in Children with Asthma: A Systematic Review General comment This article aims to review the reported frequency of adverse drug reactions attributed to LTRAs in children with asthma. The authors should be congratulated for identifying this important aspect of paediatric pulmonology and undertaking this work. The study protocol is clear and well designed, the method used is excellent, and the results are well presented. The conclusions are acceptable. The tables are fine. The references are updated. At view, the general presentation of the article is very good. Minor comments The following comments may improve the text: - Abstract: The sentence "The aim was to…" should be moved to the Background section, so that the Method could be described in this specific section. - pag. 6, line 36: "for a diagnosis of asthma" - modify to "for asthma" - pag. 7, line 46: SmPC – spelling the acronymous at the first description - pag. 12, line 9: "elevated" – abnormal? - pag 12, line 9: "nervous system disorders" – add also psychiatric? Indeed, in the Table 3, 2nd column, Characterized ADR are not described. - I would suggest adding the following recent reference: 'de Benedictis et al., Safety of antinflammatory drugs in children with asthma, Curr Opin Allergy Immunol 2021', which adds something for ADRs of LTRAs.

VERSION 2 – AUTHOR RESPONSE

Dear Dr. Brodlie,

Thank you very much for reading my paper.

I have responded to your suggestions and uploaded my edited paper.

Kind regards,
Eleanor Dixon

VERSION 3 – REVIEW