

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Risks associated with managing asthma without a preventer: urgent healthcare and poor asthma control in a cross-sectional population survey
AUTHORS	Reddel, Helen; Ampon, Rosario; Sawyer, Susan; Peters, Matthew

VERSION 1 - REVIEW

REVIEWER	Mark Levy Part Time Sessional General Practitioner, Kenton Bridge Medical Centre, UK
REVIEW RETURNED	14-Mar-2017

GENERAL COMMENTS	<p>This is an interesting study well described and discussed. I would like to make a few recommendations for minor text amendments which I believe will highlight the importance of these survey findings:</p> <p>i) The main issue underlying this study is the concern that excess reliever use (with or without underuse of preventer medication) confers added risk of near fatal and fatal asthma attacks. Therefore I suggest the authors emphasise this in the abstract and introductory section - there are references to the Suissa papers and the NRAD as well as GINA, however the risks are not clearly spelt out.</p> <p>ii) The main disadvantage, which is acknowledged by the authors, is a common criticism of so called 'real life studies' the lack of confirmation of the asthma diagnosis in the study subjects. So there may be a number of people in both reliever only and preventer groups who do not actually have asthma - though less likely so in the preventer group because these patients will be prescribed the preventers - however the adherence to medication - and the rigour with which this is monitored by the prescribers is not known - so there may be a number of people in the preventer group who are prescribed or who are collecting insufficient medication to properly control their symptoms. I think this should be addressed in the discussion and possibly concluding section.</p> <p>This may, in my view explain the apparent two-way discrepancy between the results in the reliever and preventer groups in that overall, the reliever only group use their relievers less frequently than the preventer group; and that fewer people in the reliever only group are classified with uncontrolled asthma. I expected the opposite.</p> <p>However, there is an 'at risk group' of people within the reliever only group. The authors report on page 9, that more of those in the reliever group who accessed urgent health care were uncontrolled than those who did not. There is no way from the data, to determine</p>
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	<p>whether these people are more severe, or may be more likely to have asthma than not - however, I suggest this important (my view) finding should be included in the abstract and discussion and summary at the end. Perhaps something like: ' Those people in the reliever only group who had uncontrolled asthma were more likely to seek urgent asthma care' - and a conclusion at the end of the paper may suggest inclusion of an ACT in the packaging of SABA inhalers with a warning that people with a score under 15 should seek urgent medical help from someone with asthma expertise.</p>
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REVIEWER	FRANCISCO-JAVIER GONZALEZ-BARCALA CLINIC UNIVERSITY HOSPITAL OF SANTIAGO DE COMPOSTELA SPAIN
REVIEW RETURNED	02-May-2017

GENERAL COMMENTS	<p>IMPORTANCE OF THE QUESTION OR SUBJECT STUDIED</p> <p>The study of asthma patients who are treated with reliever only therapy is a very important topic for research</p> <p>The information provided is new.</p> <p>The objectives are clearly stated.</p> <p>ADEQUACY OF APPROACH</p> <p>The experimental design , which includes a large sample size, seems adequate</p> <p>The meaning of “points to the value of AUD 1.50 should be explained more clearly. It gives the impression that each point was paid for with 1.5 Australian dollars.</p> <p>The variables analysed should be clearly explained. E. g. household income in table 1 is classified as <52000\$ and ≥52000\$; however in the discussion section, page 16-line52, there is a reference to the</p>
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	<p>lowest quintile of household income.</p> <p>There are some important factors lacking, such as body mass index, comorbidities, work activities, etc.</p> <p>In the discussion it is stated that access to internet is lower in low income patients. These data should be described in the methods section</p> <p>In the statistical analysis one wonders what the reason for choosing a “p” level <0.002 as significant was?. Usually the threshold is 0.05</p> <p>Acceptable from an ethical point of view.</p> <p style="text-align: center;">RESULTS</p> <p>The results are difficult to read because there are some data described in the text but no clearly shown in tables nor figures. E.g. how many patients have had a non-urgent GP visit?</p> <p>What is necessary is a table showing us the main clinical characteristics of reliever-only users and preventer users: age, gender, frequency of reliever use, how many of them are well controlled,...</p> <p>The main characteristics of the patients who haven't completed the</p>
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	<p>survey should be shown and compared to those who have completed it. These data could have some impact on the results if there are any significant differences, such as older age, lower social class, etc.</p> <p>The main results of figure 2 should be explained in the main text.</p> <p>Page 15, line 6: the sentence “people don’t realise how serious asthma is” is not included in table 3.</p> <p style="text-align: center;">DISCUSSION</p> <p>In general relevant. However it is sometimes difficult to read due to the way the results are presented</p> <p>Page 17, line 52, the number of the reference (number 6 in this case) is lacking in the text.</p> <p>Page 17, lines 55-57, and page 18, lines 1-3 should be included in the results section rather than in the discussion.</p> <p style="text-align: center;">REFERENCES</p> <p>Relevant and updated.</p> <p style="text-align: center;">GRAMMAR AND STYLE</p>
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It is sometimes difficult to follow due to the way the results are presented.

ABSTRACT

Adequate and well structured.

Only a few minor concerns because the objectives stated in the abstract are not the same as those in the main text: “to examine the characteristics of those only using a relieve” is not in the abstract.

Line 31-33: It is stated “only 36.0% had a non-urgent asthma review”. However the meaning of this sentence is not clear, because according to table 2, 71% have “no urgent asthma healthcare”. However, according to the data shown on page 10, lines 19-26, 66.6% of patients with urgent health care and 26.7% of patients without urgent healthcare have had a non-urgent GP visit, which makes 35.9%, however, this result is not clearly shown in the text, which means the reader has to make a careful calculation

Line 38: $P < 0.009$ in the abstract, but in table 2, $p = 0.009$

The last paragraph “Reliever-only users purchasing reliever over-the-

counter were no more likely than those using prescriptions to have uncontrolled asthma (34.2% vs 38.1%, $p = 0.19$), but were less likely to have had a non-urgent asthma review”, is rather confusing because it is not clear whether the comparison is between patients purchasing relievers OTC with patients who purchase relievers with medical order or with patients who have preventer treatment.

On top of this, these data are not shown in the main text.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

R1.1. The main issue underlying this study is the concern that excess reliever use (with or without underuse of preventer medication) confers added risk of near fatal and fatal asthma attacks.

Therefore I suggest the authors emphasise this in the abstract and introductory section - there are references to the Suissa papers and the NRAD as well as GINA, however the risks are not clearly spelt out.

A1.1. We appreciate the opportunity to add more detail about the risk of overuse of SABAs.

For the Abstract, the strict word count restriction precludes much detail, but within these limits, we have changed the first sentence to: "Overuse of asthma relievers, particularly without anti-inflammatory preventers, increases asthma risks." In the Introduction, we have added this text: "In the 1980s, overuse of SABAs was associated with an epidemic of asthma deaths in several countries including Australia,{Abramson, 2001} and dispensing of ≥ 12 inhalers in a year was associated with increased risk of asthma-related death.{Suissa, 1994}". We have also added the word "still" to the following sentence: "However, despite more than 25 years of guideline development and messaging targeting both patients and healthcare providers, it is thought that a significant proportion of those living with asthma still rely, to their detriment, on SABAs as their sole asthma treatment". In the Discussion on page 19, we have added a further reference to the contribution to fatal asthma (with the above Suissa reference), and have added an additional reference (Stanford et al, 2012) about the association between overuse of SABA and exacerbations.

R1.2. The main disadvantage, which is acknowledged by the authors, is a common criticism of so called 'real life studies' the lack of confirmation of the asthma diagnosis in the study subjects. So there may be a number of people in both reliever only and preventer groups who do not actually have asthma - though less likely so in the preventer group because these patients will be prescribed the preventers - however the adherence to medication - and the rigour with which this is monitored by the prescribers is not known - so there may be a number of people in the preventer group who are prescribed or who are collecting insufficient medication to properly control their symptoms. I think this should be addressed in the discussion and possibly concluding section.

A1.2. The limitations are acknowledged, including that both reliever-only and preventer groups may have included participants who, despite having been given an asthma diagnosis, did not in fact have asthma. However, as reported in the manuscript, the group of participants who only used a reliever medication had a concerning frequency of poor asthma control and acute asthma events. If, within that pool, some participants did not have asthma and were therefore at negligible risk of such adverse events, the risk measures for participants with "true asthma" taking reliever only may therefore be under-estimated. To run this argument hard in a manuscript would be an overuse of conjecture!

We agree with the comment about adherence – clinicians often assume that patients are continuing to take a prescribed preventer, yet from dispensing studies, the majority of patients fail to renew their preventer after the first prescription (e.g. of patients with an initial prescription for salmeterol/fluticasone in Bender et al, JACI 2006;118:899-904, 59% never filled it again over a 12 month period). This means that in clinical practice, patients taking reliever-only treatment may not be recognised as such, unless the clinician asks in a sensitive way about the treatment they are taking. On page 18, we have added: "...clinicians are often unaware that many patients fail to renew their preventer prescription {Stirratt, 2015}" and on page 19, "However, patients may be reluctant to say that they have stopped taking their preventer" (with the same reference). In the concluding section (page 21), in the description of the potential impact of any brief contact with a health professional, we have added that this could include "an empathic discussion about current treatment".

R1.3. This may, in my view explain the apparent two-way discrepancy between the results in the reliever and preventer groups in that overall, the reliever only group use their relievers less frequently

than the preventer group; and that fewer people in the reliever only group are classified with uncontrolled asthma. I expected the opposite.

A1.3. This cannot be fully explored in a cross-sectional study. However, we believe that the most likely explanation for these findings is confounding by severity. In addition, the reliever-only group is heterogeneous, including patients who, by any assessment, should be prescribed a preventer treatment, and others who by current guidelines would not be considered to benefit from such treatment, and some who, had they undergone testing, may have been proven not to have asthma at all.

R1.4. However, there is an 'at risk group' of people within the reliever only group. The authors report on page 9, that more of those in the reliever group who accessed urgent health care were uncontrolled than those who did not. There is no way from the data, to determine whether these people are more severe, or may be more likely to have asthma than not - however, I suggest this important (my view) finding should be included in the abstract and discussion and summary at the end. Perhaps something like: ' Those people in the reliever only group who had uncontrolled asthma were more likely to seek urgent asthma care' - and a conclusion at the end of the paper may suggest inclusion of an ACT in the packaging of SABA inhalers with a warning that people with a score under 15 should seek urgent medical help from someone with asthma expertise.

A1.4. We agree that poor recent symptom control is a strong predictor of risk of exacerbations. Unfortunately the word count restriction for the abstract precludes the addition of the suggested comment - unless the Editor will permit us to go a few words over the limit of 300 words. However, we have added the interesting suggestion about including ACT in the packaging of SABA inhalers on page 21. "Further, a quick screening tool for asthma symptom control^{10,33} could be included, with interpretive advice, inside SABA packaging."

Reviewer 2

R2.1. IMPORTANCE OF THE QUESTION OR SUBJECT STUDIED

The study of asthma patients who are treated with reliever only therapy is a very important topic for research. The information provided is new. The objectives are clearly stated.

No response required.

ADEQUACY OF APPROACH

R2.2. The experimental design, which includes a large sample size, seems adequate.

No response required

R2.3. The meaning of "points to the value of AUD 1.50 should be explained more clearly. It gives the impression that each point was paid for with 1.5 Australian dollars.

A2.3. Members of web-based panels do not receive cash payments for completing a survey, but instead, are given a certain number of 'points' which can be redeemed later for a store voucher e.g. for a CD. In the present case, participants who completed the survey received points that had an effective value (if redeemed) of \$1.50 Australian dollars. The wording has been clarified to "points with a value of AUD 1.50, that were redeemable for small items but not cash". This amount was so small as to be very unlikely to result in response bias.

R2.4. The variables analysed should be clearly explained. E. g. household income in table 1 is classified as <52000\$ and ≥52000\$; however in the discussion section, page 16-line 52, there is a reference to the lowest quintile of household income.

A2.4. The statement in the discussion section on page 17 is about home internet access and household income for Australia as a whole rather than for the present study. We apologise that the relevant reference from the Australian Bureau of Statistics was inadvertently omitted; it has now been added.

R2.5. There are some important factors lacking, such as body mass index, comorbidities, work activities, etc.

A2.5. The data presented in this manuscript are from a patient-completed questionnaire, so data for BMI are not available. It would have been interesting to know about comorbidities and occupation, but these questions were not asked in the survey.

R2.6. In the discussion it is stated that access to internet is lower in low income patients. These data should be described in the methods section.

A2.6. As indicated in A2.4, the statement about access to internet in the discussion relates to Australia as a whole, not the present survey. We trust that the addition of the missing reference (as described in A2.4 above) should avoid any confusion.

R2.7. In the statistical analysis one wonders what the reason for choosing a “p” level <0.002 as significant was?. Usually the threshold is 0.05

A2.7. As indicated in the Methods, a Bonferroni correction was made for multiple testing. This was done in order to avoid Type I errors. We took a conservative approach: since around 25 variables were analysed, the usual p value of 0.05 was divided by 25, giving a threshold of 0.002.

R2.8. Acceptable from an ethical point of view.

No comment required

RESULTS

R2.9. The results are difficult to read because there are some data described in the text but no clearly shown in tables nor figures. E.g. how many patients have had a non-urgent GP visit?

A2.9. We followed the usual publishing convention that data in tables/figures should not be exactly duplicated in the text. However, in response to this comment and the one below, we have added extra clinical details to Tables 1 and 2, including the proportion of participants who had a non-urgent GP visit.

R2.10. What is necessary is a table showing us the main clinical characteristics of reliever-only users and preventer users: age, gender, frequency of reliever use, how many of them are well controlled,...

A2.10. Age and gender were already reported in Tables 1 and 2, but, as above, we have now added the frequency of reliever use, ACT score, % with good asthma symptom control, and overall health status.

R2.11. The main characteristics of the patients who haven't completed the survey should be shown and compared to those who have completed it. These data could have some impact on the results if there are any significant differences, such as older age, lower social class, etc.

A2.11. We do not have access to data about patients who did not complete the survey. However, given the very high completion rate (89%), there would have been little potential for bias in this study compared with results from other surveys using paper or telephone questionnaires. For example, in the national US asthma survey described in reference #7, completed survey forms were returned by mail by only 61% of the study population. In a 2003 Australian asthma survey which recruited participants by random digit dialling (Marks et al, *Respirology* 2007), only 34% of people contacted agreed to answer the screening survey, and from amongst those, the survey was completed by only 69% of those identified as having current asthma, giving a completion rate of 23%.

R2.12. The main results of figure 2 should be explained in the main text.

A2.12. The main results of Figure 2 were described in the Results section, in the first paragraph after Table 2 (“participants with poor current symptom control were more likely to have required urgent healthcare in the previous year (Figure 2)”). We have now also added the percentages of participants who had any urgent health care (42.1% vs 11.6%). Figure 2 would be expected to be positioned near

to this text, so we have not duplicated the results for sub-categories that are shown, with percentages, in the figure.

R2.13. Page 15, line 6: the sentence “people don’t realise how serious asthma is” is not included in table 3.

A2.13. Thank you for pointing out this omission. The result has been added to Table 3.

DISCUSSION

R2.14. In general, relevant. However it is sometimes difficult to read due to the way the results are presented.

A2.14. The text has been clarified where requested.

R2.15. Page 17, line 52, the number of the reference (number 6 in this case) is lacking in the text.

A2.15. Thank you for identifying this omission. The reference has been restored.

R2.16. Page 17, lines 55-57, and page 18, lines 1-3 should be included in the results section rather than in the discussion.

A2.16. This result was shown in Figure 2. However, as indicated above in A2.12, the percentage has now also been added to the Results text.

REFERENCES

R2.17. Relevant and updated.

No response required.

R2.18. GRAMMAR AND STYLE

It is sometimes difficult to follow due to the way the results are presented.

A2.18. The text has been clarified where requested.

ABSTRACT

R2.19. Adequate and well structured. Only a few minor concerns because the objectives stated in the abstract are not the same as those in the main text: “to examine the characteristics of those only using a reliever” is not in the abstract.

A2.19. The strict word count restriction for the abstract means that the objectives cannot be stated with the same level of detail as in the text. We believe that the stated aims - to identify how many reliever-only users have urgent healthcare, explore their attitudes and beliefs about asthma and its treatment, and investigate whether purchasing reliever over-the-counter was associated with worse asthma outcomes than by prescription – enable readers to understand that we will be describing the characteristics of these patients.

R2.20. Line 31-33: It is stated “only 36.0% had a non-urgent asthma review”. However the meaning of this sentence is not clear, because according to table 2, 71% have “no urgent asthma healthcare”.

However, according to the data shown on page 10, lines 19-26, 66.6% of patients with urgent health care and 26.7% of patients without urgent healthcare have had a non-urgent GP visit, which makes 35.9%, however, this result is not clearly shown in the text, which means the reader has to make a careful calculation.

A2.20. As indicated in response A2.9 above, we have added the proportion of reliever-only users with a non-urgent review visit to Table 1 (and to Table 2).

R2.21 Line 38: $P < 0.009$ in the abstract, but in table 2, $p = 0.009$.

A2.21. The typographical error has been corrected.

R2.22. The last paragraph “Reliever-only users purchasing reliever over-the-counter were no more likely than those using prescriptions to have uncontrolled asthma (34.2% vs 38.1%, $p = 0.19$), but were

less likely to have had a non-urgent asthma review”, is rather confusing because it is not clear whether the comparison is between patients purchasing relievers OTC with patients who purchase relievers with medical order or with patients who have preventer treatment. On top of this, these data are not shown in the main text.

A2.22. Preventers were not mentioned in this sentence, so we are not sure why there may be confusion. However, to avoid any possible ambiguity, we have changed the text to “Reliever-only users purchasing relievers over-the-counter were no more likely than those purchasing relievers by prescription...”. We also corrected a typographical error in the abstract, which may have been the reason that this result appeared not to be in the main text. The correct result was “(35.9% vs 40.6%, p=0.23)”, as was reported in the main text.

VERSION 2 – REVIEW

REVIEWER	Mark Levy Independent Sessional General Practitioner Respiratory Clinical Lead Harrow Clinical Commissioning Group, United Kingdom
REVIEW RETURNED	05-Jun-2017

GENERAL COMMENTS	<p>The paper is well written and clear.</p> <p>I have one suggestion for the authors to consider - thats why I scored 'minor revision' above:</p> <p>While it is clear and interesting that, the study investigates characteristics and outcomes of people using relievers only, the authors have not discussed the comparative results between the reliever only and preventer groups. discussion As a result, a reader may get the impression that patients using preventers do as badly as those using relievers only (P values for reliever use, ACT and control in Table 1)</p> <p>My suggestion for the authors would be to discuss this observation - and provide possible reasons explaining for e.g. why overall the preventer group used more reliever medication than the reliever only group - Table 1 and had similar ACT scores to the reliever only group - Figure 1.</p> <p>I have assumed these differences may relate to the different age breakdown in the two groups, with more elderly patients in the preventer group. The differences in daily preventer group are more evident in the older patients and it may be worth considering analysing / or displaying the results by age groups (e.g. under 50 and over).</p>
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REVIEWER	FRANCISCO-JAVIER GONZALEZ-BARCALA CLINIC UNIVERSITY HOSPITAL of SANTIAGO DE COMPOSTELA
REVIEW RETURNED	28-May-2017

GENERAL COMMENTS	All my concerns were correctly addressed
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VERSION 2 – AUTHOR RESPONSE

RESPONSE TO REVIEWER COMMENTS

BMJ OPEN 2017-016688.R1: Risks associated with managing asthma without a preventer: urgent healthcare and poor asthma control in a cross-sectional population survey

Reviewer 1

R1.1. The paper is well written and clear. I have one suggestion for the authors to consider - that's why I scored 'minor revision' above: While it is clear and interesting that, the study investigates characteristics and outcomes of people using relievers only, the authors have not discussed the comparative results between the reliever only and preventer groups. As a result, a reader may get the impression that patients using preventers do as badly as those using relievers only (P values for reliever use, ACT and control in Table 1) My suggestion for the authors would be to discuss this observation - and provide possible reasons explaining for e.g. why overall the preventer group used more reliever medication than the reliever only group - Table 1 and had similar ACT scores to the reliever only group - Figure 1. I have assumed these differences may relate to the different age breakdown in the two groups, with more elderly patients in the preventer group. The differences in daily preventer group are more evident in the older patients and it may be worth considering analysing / or displaying the results by age groups (e.g. under 50 and over).

A1.1. Thank you for these comments. The apparent discrepancies noted above are explained by the heterogeneity of the reliever-only group, which included many patients with very infrequent symptoms and infrequent reliever use. For example, in Table 1, 25% used reliever "a few times a year" and a further 11% used it "less than one day a month"; and in Figure 1, ~16% of reliever-only users had perfect ACT scores (25/25) for asthma symptom control in the previous 4 weeks, indicating no symptoms, activity limitation, night waking or reliever use during that time. However, the reliever-only group also included many patients who clearly had uncontrolled asthma and were at high risk of urgent healthcare, and this is the group upon which the manuscript is primarily focused, as they are clearly in need of regular preventer treatment.

To clarify these issues, and to highlight the heterogeneity of the reliever-only group, we have added median and IQR data for ACT scores to Tables 1 and 2; and we have added a comment in the Results on page 9 that the distribution of ACT scores for reliever-only users in Figure 1 was heterogeneous. Table 2 also shows that for reliever-only users with and without urgent healthcare in the previous 12 months, there was a 6 point difference in median ACT score for symptom control in the 4 weeks before the survey (16 vs 22 respectively, $p < 0.0001$). In the first paragraph of the Discussion, we have strengthened the statement about variation within the reliever-only group, as follows (new text underlined): "Although some of these patients appear to have mild asthma, there was marked heterogeneity within the population, and it was a concern to find that, in the previous year, almost one quarter of the 1038 reliever-only participants had required urgent healthcare for asthma, and only one third had a non-urgent GP review of their asthma."

However, we agree with the Reviewer that the data for ACT scores and reliever use in Table 1 (which had been added in the previous revision at the request of Reviewer 2) could be misinterpreted as suggesting that preventers are not effective. Instead, these differences in asthma symptom control and reliever use are highly likely to be explained by confounding by indication (i.e. by severity). Additional potential contributors include incorrect inhaler technique and comorbidities; these are issues to which cross-sectional symptom questionnaires are insensitive. To address the concerns of Reviewer 1, we have therefore expanded the comments about these data as follows, on page 18 of the Discussion:

"Limitations, as for any survey, were that the diagnosis of asthma could not be confirmed objectively, and that cross-sectional comparisons between reliever-only and preventer users may be confounded by severity. It would be a mistake to suggest from these data that preventer therapies are ineffective,

given the underlying severity of disease that led to a preventer being prescribed, that poor adherence and inhaler technique may have limited its benefit, and that comorbidities such as obesity may have contributed to respiratory symptoms particularly amongst preventer users, who were older.”

Finally, with regard to agegroup, exploratory analysis revealed that its independent contribution to reliever use and ACT scores was very small, so to avoid adding complexity to the manuscript, we have not added an extra table with results divided by age-group. Instead, we have mentioned age-group as a potential contributory factor in the statement above in the Discussion, and have drawn attention to the over-representation of older patients amongst preventer users.

Reviewer 2

All my concerns were correctly addressed

Thank you.