SUPPLEMENTARY MATERIAL

Appendix S1

METHODS

Statistical methods (secondary outcomes)

Secondary outcomes included total duration and severity of 12 symptoms up to 28 days; duration of moderately bad/worse and any cough up to 56 days; duration of abnormal peak flow; antibiotic consumption; adverse events and participant satisfaction with treatment.

Secondary outcomes were analysed as per the OSAC trial for the main analysis group only. These were performed by plotting the daily symptom score against time, up to 28 days, to allow calculation of area under the curve for each symptom. Linear regression (adjusting for presence of relevant symptom at baseline) was used to compare prednisolone and placebo groups. For those who had unresolved cough at 28 days, Cox proportional hazard models considered time to resolution of moderately bad or worse cough and time to complete resolution adjusting for prior duration of cough. Duration of abnormal peak-flow was compared to the expected peak flow for the participant's gender, age and height. A definition of <80% of expected was used to define abnormal. Antibiotic consumption was analysed using logistic regression (adjusting for delayed prescription).

Participants were recorded as having experienced none, one, or more than one adverse event by treatment group and compared using ordinal logistic regression, adjusting for center and baseline impression of illness. The odds ratios of these models represent the likelihood of a worse outcome among the range of possible categories (0, 1, >1 event). Patient satisfaction was analysed using logistic regression models to compare the amount of patients in each group who agreed or disagreed to the following two statements 1) my OSAC trial tablets helped me to feel better from my cough and 2) I would want to take my OSAC tablets again if I developed another similar chesty cough in the future.

RESULTS

In the sensitivity analysis group, participants had a mean age of 50.9 (SD, 17.9) years; 48% were male, 19% were current smokers and 43% had abnormal peak flow (Supplementary Table S1).

Primary outcomes (sensitivity analyses)

Moderately bad or worse cough

In the sensitivity analysis group, data were available for 17 of 21 participants (81%), with three reporting an initial cough severity of less than three points and one lost to follow up. The median duration of moderately bad or worse cough was three days for both prednisolone (IQR, 1-4) and placebo (IQR, 1-7). As with the main analysis group, Kaplan Meier survival curves showed no clinically important differences between prednisolone and placebo (Supplementary Figure S1), and visual inspection of log-log survival curves and calculation of the Schoenfeld residuals provided no evidence against proportional hazards. When adjusting for centre and baseline cough duration, this produced a hazard ratio of 0.82 (95% CI 0.22, 3.01) comparing prednisolone with placebo (P=0.76). The adjusted Weibull AFT model time ratio was 1.20 (95% CI 0.47, 3.12) indicating that the time to resolution was increased by 20% (0.6 days) with prednisolone compared to placebo (P=0.70), with 95% confidence intervals showing this could have been as much as 1.59 days shorter or 6.36 days longer, i.e. outside the MCID. Secondary additional adjustment was not made due to the small sample size.

Symptom severity

Data were available for 20 (95%) participants. In the sensitivity analysis group, when adjusting for centre and baseline illness severity, there was a mean symptom severity reduction of -0.31 (95% CI -1.22, 0.59, P=0.48) between prednisolone and placebo, also within the MCID of 1.66. Secondary additional adjustment was not made due to the small sample size.

Diagnoses of asthma at 3-months follow up

Interestingly, of the 398 patients who participated in the OSAC trial, three went on to receive an asthma diagnosis during a three month follow up in the original study. One of these met the criteria for clinically unrecognised asthma in the current analysis, answering yes to the presence of wheeze, nocturnal cough and chest tightness. Of the other two patients, one answered yes to the presence of wheeze, night cough and shortness of breath during the day, and the other answered yes only to night cough. Although the criteria used to detect clinically unrecognised asthma correctly predicted one diagnosis of asthma at three months, its failure to detect the other two others highlights a potential weakness of the definition used.

Supplementary Table S1. Baseline characteristics (sensitivity analysis groups)

	Sensitivity analysis group (N=21)		**Rest of OSAC sample** (N=377)
	Prednisolone (N=10)	**Placebo** (N=11)	
Centre, n (%)			
Bristol	8 (80%)	5 (45.4%)	218 (57.8%)
Oxford	1 (10%)	3 (27.3%)	80 (21.2%)
Southampton	1 (10%)	0 (0%)	44 (11.7%)
Nottingham	0 (0%)	3 (27.3%)	35 (9.3%)
Demographics and past medical history			
Gender, n (%) male	6 (60%)	4 (36.4%)	138 (36.6%)
Age, mean (SD)	61.6 (13.7)	41.2 (16.1)	47.2 (15.9)
Weight kg, median (IQR)	80.5 (74.0, 95.0)	91.0 (70.0, 97.0)	76.0 (65.0, 90.0)
Height cm, median (IQR)	167.0 (160.0, 176.0)	171.0 (166.0, 177.0)	168.0 (162.0, 175.0)
Ethnicity, n (%) white	10 (100%)	10 (90.9%)	361 (96%)
Occupation, n (%)			
Employed	6 (60%)	6 (54.6%)	268 (71.1%)
Unemployed	1 (10%)	2 (18.2%)	15 (3.9%)
Retired	2 (20%)	2 (18.2%)	67 (17.8%)
Other	1 (10%)	1 (9.1%)	27 (7.2%)
Deprivation (IMD), median (IQR) [a]	8.5 (4, 22)	12 (9, 23)	11 (5, 23)
Smoking status, n (%)			
Current	1 (10%)	3 (27.3%)	65 (17.3%)
Past	2 (20%)	6 (54.6%)	110 (29.3%)
Never	7 (70%)	2 (18.2%)	201 (53.5%)
Lives with smoker, n (%) [b]	0 (0%)	5 (50%)	52 (14.5%)
Received asthma medication >5 years previously [c]	0 (0%)	1 (9.1%)	17 (4.7%)
Personal history of hay fever [d]	4 (50%)	3 (30%)	80 (22.3%)
Personal history of eczema [e]	1 (11.1%)	3 (27.3%)	52 (14.7%)
Family history asthma/hay fever/eczema, n (%) [f]	4 (44.4%)	8 (72.7%)	137 (39%)
Influenza vaccine in last 12 months, n (%)	4 (40%)	3 (27.3%)	100 (26.5%)
Recruited in winter (1st Oct-31st March)	6 (60%)	6 (54.6%)	214 (56.8%)
Clinical characteristics and management			
Prior duration of cough, median (IQR) days	11 (7, 17)	17 (10, 21)	10 (6, 19)
Sputum (symptom <24hr), n (%)	5 (50%)	9 (81.8%)	291 (77.4%)
Shortness of breath (symptom <24hr) n (%)	8 (80%)	7 (63.6%)	264 (70%)
Wheeze (symptom <24hr), n (%)	8 (80%)	7 (63.6%)	171 (45.5%)
Chest pain (symptom <24hr) n (%)	3 (30%)	6 (54.6%)	176 (46.7%)
Patient reported illness severity (0-10), median (IQR) [g]	7 (4, 7)	5 (3, 5)	6 (4, 7)
Pulse rate (bpm), mean (SD)	69.7 (14.4)	81.2 (8.55)	77.9 (12.01)
Temperature (^{o}C), mean (SD)	36.5 (0.4)	36.6 (0.55)	36.6 (0.5)
Oxygen saturation (%), mean (SD)	97.3 (1.8)	97.8 (0.6)	97.66 (1.2)
Baseline abnormal peak flow	6 (60%)	3 (27.3%)	157 (41.8%)
Abnormal respiratory rate, n (%)	0 (0%)	0 (0%)	3 (1%)
Chest recession/prolonged expiration	0 (0%)	0 (0%)	1 (1%)
Wheeze/rhonchi (auscultation), n (%)	2 (20%	2 (18.2%)	18 (4.8%)
Crackles/crepitations (auscultation), n (%)	1 (10%)	0 (0%)	9 (2.4%)
Bronchial breathing	0 (0%)	1 (9.1%)	1 (1%)
Taken prescribed β agonist in past 24 hours, n (%)	2 (20%)	1 (9.1%)	9 (2.4%)
OTC[q] drugs taken for current cough, n (%)	4 (40%)	6 (54.6%)	257 (68.2%)
Given delayed antibiotic script, n (%) [h]	2 (20%)	2 (18.2%)	43 (11.4%)

Abbreviation: IQR, interquartile range

[a] English Index of Multiple Deprivation scores (range, 0-100; higher scores indicate higher levels of deprivation). Data missing for 1 in placebo group

[b] Living with smoker data missing for 1 in the prednisolone group and 1 in the placebo group

[c] Data on use of asthma medication >5 years previously missing for 1 patients in the prednisolone group

[d] Personal history of hayfever data missing for 2 in the prednisolone group and 1 in the placebo group

[e] Personal history of eczema data missing for 1 in the prednisolone group

[f] Family history of hay fever, eczema or asthma data missing for 1 in the prednisolone group

[g] Patient-reported illness severity scores: 0 (completely well) to 10 (extremely unwell)

[h] Delayed antibiotic script data missing for 1 in the placebo group

Supplementary Table S2. Primary outcomes (sensitivity analysis groups)

	Prednisolone		Placebo		Prednisolone vs. placebo	
	N	Median (IQR)	N	Median (IQR)	HR (95% CI); P value	Time Ratio[a] (95% CI); P value
Duration of moderately bad/worse cough[b]	8	3 (1, 4)	9	3 (1, 7)		
Unadjusted					1.20 (0.43, 3.34); P=0.72	0.79 (0.30, 2.11); P=0.65
Adjusted for centre and baseline cough duration[b]					0.82 (0.22, 3.01); P=0.76	1.20 (0.47, 3.12); P=0.70
	N	Mean (SD)	N	Mean (SD)	Difference in means (95% CI); P value	
Mean symptom severity score (days 2-4)[c]	10	1.81 (0.91)	10	1.97 (0.99)		
Unadjusted					-0.17 (-1.06, 0.73); P=0.70	
Adjusted for centre and baseline illness severity[b]					-0.31 (-1.22, 0.59); P=0.48	

[a] Time ratio can be interpreted as the relative increase or decrease in time to resolution from moderately bad or worse cough in the prednisolone vs. the placebo group

[b] Baseline measure of duration of cough is prior duration of cough (1-28 days) and of mean symptoms severity score is patient-reported illness severity (range 0-10)

[c] See methods section for derivation of mean symptoms severity score (0 [least severe] to 6 [most severe])

Supplementary Box S1: International Primary Care Airways Group Adult Asthma Questionnaire

Adult Asthma Questionnaire

Instructions: To evaluate the possibility of asthma in adults age 15 and over, start by asking the questions below. Given the intermittent nature of asthma symptoms, these questions may need to be asked repeatedly over time to establish the likelihood of asthma.

This questionnaire contains the questions related to asthma symptoms and risk factors that have been identified in peer-reviewed literature as having the greatest diagnostic value. It will not produce a definitive diagnosis, but may enable you to determine whether a diagnosis of asthma should be further investigated or is unlikely.

Adult Asthma Questionnaire		
Question	**Response Choices**	
1. Have you had wheezing or whistling in your chest at any time in the last 12 months?	**Yes**	No
2. Have you been woken up at night by an attack of shortness of breath at any time in the last 12 months?	**Yes**	No
3. Have you been woken up at night by an attack of coughing at any time in the past 12 months?	Yes	No
4. Have you woken up with a feeling of tightness in your chest at any time in the last 12 months?	Yes	No
5. Have you had an attack of shortness of breath that came on following strenuous activity at any time?	Yes	No
6. Have you had an attack of shortness of breath that came on during the day when you were at rest at any time?	Yes	No
7. If you answered "Yes" to any of the questions above, do your symptoms occur less frequently or not at all on days away from work and on vacations?	Yes	No

REFERENCES: Abramson MJ, Hensley MJ, Saunders NA, Wlodarczyk JH. Evaluation of a new asthma questionnaire. *J Asthma* 1991;28:129-39. Burney PG, Laitinen LA, Perdrizet S, Huckauf H, Tattersfield AE, Chinn S, et al. Validity and repeatability of the IUATLD (1984) Bronchial Symptoms Questionnaire: an international comparison. *Eur Respir J* 1989;2:940-5. Ravault C, Kauffmann F. Validity of the IUATLD (1986) questionnaire in the EGEA study. International Union Against Tuberculosis and Lung Disease. Epidemiological study on the Genetics and Environment of Asthma, bronchial hyperresponsiveness and atopy. *Int J Tuberc Lung Dis* 2001;5:191-6. Sistek D, Tschopp J-M, Schindler C, et al. Clinical diagnosis of current asthma: predictive value of respiratory symptoms in the SAPALDIA study. Swiss Study on Air Pollution and Lung Diseases in Adults. *Eur Respir J* 2001;17:214-9.

Evaluation:

- A positive response to any of the questions 1-6, particularly questions 1 or 2 in bold, suggests an increased likelihood of asthma. The more positive answers, the greater the likelihood of asthma. If in your judgement the patient's responses suggest asthma, proceed to the Adult Asthma Diagnosis Guide, page 10.
- A positive response to question 7 suggests an occupational association. Referral of the patient to a specialist for further objective testing and assessment is recommended.
- If answers suggest asthma is unlikely, consider other diagnoses or specialist referral.

Supplementary Box S2: OSAC Study Questionnaire

4.3 PAST MEDICAL AND FAMILY HISTORY (NB: Validated questions - wording of questions must be used exactly as written)

Thinking back to the 12 months before your current illness started:

1. Have you had wheezing or whistling in your chest at any time in the last 12 months? ☐ Yes ☐ No
2. Have you been woken up at night by an attack of shortness of breath at any time in the last 12 months? ☐ Yes ☐ No
3. Have you been woken up at night by an attack of coughing at any time in the last 12 months? ☐ Yes ☐ No
4. Have you woken up with a feeling of tightness in your chest at any time in the last 12 months? ☐ Yes ☐ No
5. Have you had an attack of shortness of breath that came on following strenuous activity at any time? ☐ Yes ☐ No
6. Have you had an attack of shortness of breath that came on during the day when you were at rest at any time? ☐ Yes ☐ No
7. If the answer to any of the above is **"Yes"**, do your symptoms occur less frequently or not at all on days away from work and on vacations? ☐ Yes ☐ No
8. Does the weather affect your cough? ☐ Yes ☐ No ☐ No cough
9. Do you ever cough up phlegm (sputum) from your chest when you do not have a cold? ☐ Yes ☐ No
10. Do you usually cough up phlegm (sputum) from your chest first thing in the morning? ☐ Yes ☐ No
11. How frequently do you wheeze? ☐ Occasionally or more often ☐ Never
12. Do you or another member of your family have any history of eczema? ☐ Yes ☐ No ☐ Don't know
    If yes, please tick as many as apply: ☐ You ☐ Parent ☐ Sibling
13. Do you or another member of your family have any history of hay fever? ☐ Yes ☐ No ☐ Don't know
    If yes, please tick as many as apply: ☐ You ☐ Parent ☐ Sibling
14. Do you or another member of your family have any history of asthma? ☐ Yes ☐ No ☐ Don't know
    If yes, please tick as many as apply: ☐ You* ☐ Parent ☐ Sibling

*** If the patient has taken medication for asthma within the past 5 years, they should be excluded from the OSAC trial.**

Supplementary Figure S1. Kaplan-Meier Analysis of Time to Recovery from Moderately Bad or Worse Cough (sensitivity analysis groups)