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Are smokers with acute cough in primary care prescribed antibiotics more often, and to what benefit? – An observational study in 13 European countries

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Abstract

Background: Little is known about actual clinical practice regarding management of smokers compared to ex-smokers and non-smokers presenting with acute cough in primary care, and whether a lower threshold for prescribing antibiotics benefits smokers.

Methods: This was a multi-centre 13 country European prospective observational study of primary care clinician management of acute cough in consecutive immunocompetent adults presenting with an acute cough of ≤ 28 days duration.

Results: There was complete smoking status data for 2549 of 3402 participants. 28% were smokers, 24% ex-smokers and 48% non-smokers. Smokers and ex-smokers had more chronic respiratory conditions (18.5% and 20.5% versus 12.5%). Median symptom severity scores were similar. Smokers were prescribed antibiotics more frequently (60%) than ex-smokers (51%) and non-smokers (53%). After adjusting for clinical presentation and patient characteristics, the odds ratio of being prescribed antibiotics for smokers compared to non-smokers was 1.44, 95% CI: (1.12-1.86); p value = 0.005. Patient recovery was not significantly different for smokers and non-smokers, after adjusting for clinical presentation and patient characteristics.

Conclusion: Smoking status was used as an independent factor to determine whether or not to prescribe an antibiotic. Being prescribed an antibiotic was not associated with recovery in smokers.

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Introduction

Smoking increases risk for many diseases including cardiovascular and respiratory diseases and many types of cancer. People who smoke are more likely to die at an earlier age from most illnesses compared to non-smokers.[1]

Since clinicians are aware of the association between smoking and increased risk for disease and complications, they may treat smokers more aggressively when they develop a respiratory infection compared to otherwise comparable non-smokers. [2] [3] [4]

Smokers have more frequent respiratory tract infections than non-smokers.[5, 6] Smokers are also more likely to develop pneumonia than non-smokers.[5, 7, 8] There is no consensus about whether the course of an acute cough is prolonged in smokers; one observational study suggested there is no difference compared to non-smokers [9] another suggested coughs last longer.[10]

Antibiotic resistance is increasing, driven by antibiotic prescribing. [11] Clinicians are therefore encouraged to better target antibiotic prescriptions to only those who will benefit, but there is insufficient evidence about which subgroups of patients with respiratory infections these are.[12, 13]

This evidence gap is one reason why there is wide variation in antibiotic prescribing for both upper and lower respiratory tract infections.[2, 3, 14-17] Our searches revealed no randomised placebo-controlled trials of antibiotic treatment for acute

cough in smokers. A review using data on smokers included in larger trials concluded that there was insufficient data for meta-analysis. Subset analysis concluded that "any benefit of antibiotics for smokers is the same or less for smokers than for non-smokers".[18]

We therefore used data from a 13-country, primary care observational study of acute cough presentation, management, and outcomes to investigate whether clinicians were more likely to prescribe antibiotics for smokers compared to ex-smokers and non-smokers presenting with acute cough, comparing symptom severity scores at presentation and recovery course for each smoking status category.

Methods

Genomics to combat Resistance against Antibiotics in Community-acquired lower respiratory tract infection (LRTI) in Europe (GRACE) is a network of excellence, with the aim to combat antimicrobial resistance through improved management of community-acquired LRTI (https://www.grace-lrti.org/portal/en-GB/). The first GRACE clinical study described differences in clinical presentation, management (more specifically, antibiotic prescribing) and recovery of patients consulting with an acute or worsened cough as the main or dominant symptom (or signs and symptoms suggestive of LRTI) in 14 primary care networks in 13 countries across Europe.[19] We conducted further analyses on this data set to explore our study question.

Consecutive immunocompetent patients, 18 years or older, consulting for the first time in the illness episode with an acute cough of less than 28 days duration were

eligible for inclusion. Following informed consent, the clinician completed a case report form (CRF) and the patient completed a daily symptom diary for 28 days. CRF data included presenting symptoms, as well as their severity, perceived diagnosis and management/treatment given. Patient diary data included symptom severity scores in the 28 days following the consultation, further demographic details and past medical history along with information on smoking status. Diaries with complete smoking status data were matched to their respective CRF.

Three smoking status categories were defined (Box 1). Since there are no standard definitions of "ex-smoker", we combined a definition used by the American Morbidity and Mortality Monthly cross-sectional survey to define an "ever-smoker" and combined this with a cut-off of at least one year of stopping smoking because of the high relapse rates in smokers who re-start smoking soon after quitting. [20, 21] Throughout all analyses non-smokers are used as the reference category.

Smoking status was also examined using pack years.[22] These were calculated for patients who smoked cigarettes only, since we did not have information on the weight of rolled tobacco smoked, nor is there consensus on the amount of tobacco in cigars or cigarillos. Patients who had never smoked have a pack year score of zero.

Clinicians classified the severity of 14 symptoms for each patient on a four point scale. These symptoms were: cough, phlegm, shortness of breath, wheeze, coryza, fever, chest pain, muscle ache, headache, disturbed sleep, feeling generally unwell, interference with normal activities, confusion/disorientation, and diarrhoea. Patients were asked to rate the same symptoms except for confusion/disorientation and

diarrhoea daily for up to 28 days. In addition, patients were asked about interference with social activities. Clinicians therefore rated 14 symptoms at presentation and patients rated 13 each day. All patient-reported symptoms were on a seven-point scale.

Both clinician-rated (from the CRF) and patient-rated (from the diary) total symptom severity scores were calculated by summing the individual symptom scores for each individual and scaling them to range between 0 and 100.

Analysis

Descriptives

Descriptive statistics are presented for each smoking status category by network and overall. They were calculated using mean and standard deviation (SD), median (IQR) and proportions as appropriate. Presented SDs have been inflated for clustering at the clinician level.

Modelling

Antibiotic Prescribing

Two level logistic regression (patients nested within clinicians) was used to assess the association between smoking status and antibiotic prescribing controlling for each individual clinical symptom and sign (excluding cough as this was present in 99.8% of patients), co-morbidities, age and duration of illness prior to consulting. Results are

presented as odds ratios and 95% confidence intervals. A sub-analysis was performed to assess the association between pack years and antibiotic prescribing for those individuals for whom a valid pack year estimate could be estimated.

Patient Recovery

A three-level hierarchical ARMA (1,1) model (daily symptom scores nested within individuals nested within clinicians) modelled individual total symptom severity scores (logged) over time. This model tested the association between smoking status and symptoms scores over time and interactions with antibiotic treatment. Again, a pack year sub-analysis was performed to test the association between pack years and outcome.

Results

2549 of the 3402 recruited patients (75%) had a complete clinical information and patient diary including information on their smoking status. (Figure 1).

Descriptives

702 patients (28%) were smokers. This ranged from 20 (14%) in Southampton network to 91 (42%) in Łódź network. 616 patients (24%) were classed as ex-smokers (24 (8%) in Balatonfüred network to 61 (38%) in Utrecht network). 48% of patients were classed as non-smokers (from 77 (36%) in Łódź network to 196 (66%) in Bratislava network). (Table 1).

Table 1: Countries, networks, smokers, ex-smokers and non-smokers

Country	Network	Smoker (S) % (N)	Ex-Smoker (E) % (N)	Non-Smoker (N) % (N)	OVERALL
Wales	**Cardiff**	34 (59)	29 (50)	37 (65)	174
England	**Southampton**	14 (20)	28 (40)	58 (83)	143
Netherlands	**Utrecht**	25 (39)	38 (61)	37 (59)	159
Spain	**Barcelona**	33 (56)	25 (42)	42 (70)	168
	Mataró	27 (47)	21 (37)	52 (92)	176
Germany	**Rotenberg**	28 (49)	24 (41)	48 (84)	174
Hungary	**Balatonfüred**	30 (95)	8 (24)	62 (196)	315
Belgium	**Antwerp**	42 (28)	29 (43)	43 (65)	150
Poland	**Łódź**	42 (91)	22 (47)	36 (77)	215
Italy	**Milan**	33 (50)	30 (46)	36 (55)	151
Sweden	**Jönköping**	15 (32)	36 (74)	49 (102)	208
Norway	**Tromsø**	30 (43)	32 (46)	38 (55)	144
Finland	**Helsinki**	30 (26)	25 (22)	45 (39)	87
Slovakia	**Bratislava**	19 (53)	15 (43)	66 (189)	285
OVERALL		28 (702)	24 (616)	48 (1231)	2549

There was a wide range in the number of cigarettes smoked per day among current smokers from less than 1 to 45 per day (mean 11.4, SD 7.55). The number of smoking years ranged from less than 1 to 62 years.

The median age for smokers was 44 (IQR: 33, 56) with non-smokers older, [47 (IQR: 34, 60)] and ex-smokers older still [56 (IQR: 44, 67)]. 273 patients (39%) of smokers

were men, compared to 359 (29%) of non-smokers and 280 (46%) of ex-smokers. Ex-smokers were more likely to suffer from co-existent respiratory conditions. Smokers had more respiratory illnesses compared to non-smokers. Smokers and ex-smokers were unwell for a median of 5 days, with non-smokers unwell for a median of 4 days before consulting their clinician. (Table 2).

Table 2: Patient characteristics by smoker status

PATIENT CHARACTERISTICS		Smoker N = 702	Ex-Smoker N = 616	Non-Smoker N = 1231	TOTAL N = 2549
	Gender (male) *	38.9 (273)	45.5 (280)	29.2 (359)	35.8 (912)
	Age (years) †	44 (33-56)	56 (44-67)	47 (34-60)	47 (34-60)
Co-Morbidities	Respiratory Comorbidity *, ‡	16.8 (118)	18.0 (111)	11.5 (141)	14.5 (370)
	Heart Comorbidity *, §	6.1 (43)	12.2 (75)	9.2 (113)	9.1 (231)
	Diabetes *	4.1 (29)	5.8 (36)	4.3 (53)	4.6 (118)
Symptom Information	Total number of symptoms †	8 (6-9)	8 (6-10)	8 (6-9)	8 (6-9)
	Symptom Severity Score †, ‖	31 (21-40)	30 (19-40)	29 (19-40)	29 (19-40)
	Number of days unwell before consulting †	5 (3-7)	5 (3-10)	4 (3-7)	5 (3-8)
	Number of coughs in past 12 months (lasting more than 1 week) †	2 (1-3)	2 (1-3)	2 (1-2)	1 (0-2)
Management	Prescribed Antibiotics *	60.0 (421)	51.0 (314)	53.2 (655)	54.5 (1390)
	Duration of course (days) †	7 (5-7)	7 (7-8)	7 (5-7)	7 (5-7)
Working Diagnosis	Asthma related *	2.1 (15)	2.8 (17)	2.1 (26)	2.3 (58)
	COPD related *	3.7 (26)	2.1 (13)	0.4 (5)	1.7 (44)
	Chronic Bronchitis related *	1.9 (13)	1.0 (6)	0.8 (10)	1.1 (29)
	Upper respiratory tract infection *	22.7 (159)	25.1 (154)	30.9 (379)	27.3 (692)
	Lower respiratory tract infection *	55.3 (387)	51.5 (316)	50.4 (617)	52.0 (1320)
	Other/non-specific *	14.3 (100)	17.5 (107)	15.3 (188)	15.6 (395)

* Percentage (number).
† Median (interquartile range).
‡ Respiratory comorbidity includes: Chronic Obstructive Pulmonary Disease (COPD), Asthma and Other lung disease.
§ Heart comorbidity includes: Heart failure, Ischemic heart disease and Other heart disease.
|| Symptom severity score scaled to range between 0 and 100.

Over 99% of patients had a cough. The next most common presenting symptoms were phlegm production (from 73% in non-smokers to 82% in smokers), feeling generally unwell (from 78% in ex-smokers to 82% non-smokers) and interference with normal

activities (from 68% in non-smokers and 71% in ex-smokers). A higher percentage of smokers than non-smokers presented with shortness of breath (55% vs. 46%) and wheeze (40% vs. 34%).

Overall, clinicians recorded an average of 8 symptoms for patients from the three smoking categories. The number of symptoms patients presented with recorded ranged from 1 to 14 in each category. The median severity scores of the symptoms that smokers, ex-smokers and non-smokers presented with was similar (31/100, 30/100 and 29/100 respectively). The interquartile ranges were also very similar for all groups (6-10). (Table 2).

The 14 individual symptom severity scores rated by clinicians and ranging from scores of 0-4 were similar across all smoking status categories. (Figure 2).

Working Diagnosis

Clinicians assigned each person a working diagnosis based on the history and examination findings. The proportions of patients with a working diagnosis of LRTI were not statistically different across the three smoking status categories (p-value= 0.12). (Table 2).

Clinician Views

Clinicians were asked to respond to two statements: (1) “this patient wanted me to prescribe antibiotics for them” and (2) “antibiotics will help this patient get better

quicker" using a five-point Likert-scale ranging from "strongly agree" to "strongly disagree". 48.7% of clinicians were more likely to agree or strongly agree to both these statements for smokers than non-smokers (32.7%).

Patients Views

Patients were asked to respond to several statements regarding their understanding of antibiotics on the same five-point Likert-scale. Regarding the statement "I believe that most coughs lasting more than a few days should be treated with antibiotics", smokers were more likely to agree or strongly agree than either other smoking-status category.

Antibiotic prescribing

Overall, antibiotics were prescribed for 421 (60%) smokers, 655 (53%) non-smokers and 314 (51%) ex-smokers, all for a median of 7 days. (Table 2).

Apart from Bratislava (the overall highest antibiotic prescribing network) and Barcelona (the overall lowest antibiotic prescribing network) smokers in all other networks were prescribed antibiotics more frequently than non-smokers. (Figure 3).

Antibiotic prescribing between networks and smoker categories adjusted for clinical presentation

After adjusting for variables associated with antibiotic prescribing, the OR of a smoker being prescribed antibiotics was 1.44; 95% CI (1.12-1.86); p=<0.01. Ex-

smokers had an OR of 1.18; 95% CI (0.90-1.53); p=0.23; there is insufficient evidence to show a significant difference in antibiotic prescribing between ex-smokers and non-smokers. (Table 3).

Table 3: Two level logistic regression model of antibiotic prescribing (2,519 patients nested within 123 clinicians)

			OR	Lower 95% CI	Upper 95% CI	p-value
Patient Information	Age (decades)		1.18	1.09	1.27	<0.001
	Diabetes comorbidity		1.37	0.82	2.28	0.23
	Heart comorbidity		0.89	0.59	1.34	0.57
	Respiratory comorbidity		1.33	0.97	1.81	0.07
	Smoker Status	Non-smoker	1		Reference Category	
		Current smoker	1.44	1.12	1.86	<0.01
		Ex-smoker	1.18	0.9	1.53	0.23
	Days waited before presenting		1.02	1	1.04	0.02

With the smoker status category included in the model, significant variation between networks remained, with the overall odds of antibiotic prescribing being significantly different from nine other networks (four networks prescribing more than average, five prescribing less). (Table 3).

Pack year sub-analaysis

Fitting the same model as above but including pack year values to the subgroup with valid pack years (2,346 individuals comprising 1,234 individuals who never smoked and 1,112 current or ex cigarette smokers) indicated that pack years was not a significant predictor of antibiotic prescribing (OR: 1.00, 95% CI: [0.99, 1.01]).

Patient recovery

Table 4 summarises the results of the patient recovery model. Of particular interest are the parameters related to smoking status.

The three way interaction between smoking status, being prescribed an antibiotic, and day of illness post consulting was not significant. Smokers (and ex-smokers) who are prescribed antibiotics recover at the same rate as smokers (and ex-smokers) who are not prescribed antibiotics.

Table 4: Estimates for symptom severity scores over time (63,664 symptom severity scores nested within 2,486 patients, nested within 362 clinicians)

			Value	Std. Error	p-value
Patient Characteristics	Age (decades)		0.03	0.01	0.00
	Days waited before presenting		0.01	0.00	0.00
	Diabetes comorbidity		-0.11	0.07	0.11
	Heart comorbidity		0.03	0.05	0.56
	Respiratory comorbidity		0.18	0.04	0.00
	Smoker Status	Non-smoker		Reference Category	
		Current smoker	0.09	0.07	0.16
		Ex-smoker	-0.02	0.07	0.77
Management	Not prescribed antibiotics			Reference Category	
	Prescribed antibiotics		0.07	0.06	0.19
Time	Day		-0.26	0.00	0.00
	Day squared		0.01	0.00	0.00
	Day cubed		0.00	0.00	0.00
Interactions	Prescribed Antibiotics and Day		-0.01	0.00	0.01
	Current smoker and prescribed		-0.06	0.09	0.49
	Ex smoker and prescribed		-0.04	0.09	0.70
	Smoker and Day		0.00	0.00	0.36

Ex smoker and Day	0.00	0.00	0.93
Current smoker and prescribed and day	0.00	0.00	0.50
Ex smoker and prescribed and day	0.00	0.00	0.77

Pack year sub-analysis

Fitting the same model as above but including pack years to the subset of data with valid pack year values (2,172 individuals comprising 1,154 never smokers and 1,018 current or ex cigarette smokers) indicated that patient outcome was not associated with patient pack years (coefficient: 0.001, p-value: 0.47).

Discussion

Principal Findings

We found that primary care clinicians participating in this 13 European country, observational study of the presentation, management and outcomes of acute cough prescribed antibiotics more frequently to smokers than non-smokers. This suggests that despite differences in training and practice setting, clinicians may have similar attitudes towards prescribing antibiotics for smokers.

One reason for the higher rate of prescribing for smokers may be because clinicians feel that smokers do worse if they do not receive antibiotics. However, symptom severity scores did not differ significantly at presentation or throughout recovery for smokers compared to non-smokers. Antibiotic prescribing was not associated with recovery among smokers; recovery rate was no different between smokers and non-smokers.

Strengths and Weaknesses

A double-blind randomised controlled trial would answer the question whether antibiotics benefit smokers with acute cough, however, this observational study design is best suited to describe actual clinician behaviour for a broader spectrum of patients. We were able to control for symptoms and signs, including for sicker patients receiving antibiotics more frequently.

Questions on smoking status were not included in the clinician completed CRF since we did not want to influence clinicians behaviour during the consultation. Clinicians may have had no prior knowledge of smoking status before choosing whether to prescribe antibiotics. However, since cough was an inclusion pre-requisite, we believe that the majority of clinicians would have enquired about or known about smoking status of the patient. This assumption is borne out by qualitative interviews suggesting that the majority of clinicians would enquire about smoking status during a consultation for cough (analysis in progress).

Determining criteria to define smoking status, allowing classification of participants was a complex. There is no consensus on either a clinical or a research definition of "ever-smoker" or "ex-smoker". Since relapse rates are high, the length of time since stopping smoking and defining a person as an ex-smoker varies by study; cut-off time periods produce very different results when analysing data. Similarly, there is no consensus regarding how many cigarettes need to have been smoked in a lifetime in

order to be defined as an “ever-smoker”. Pack years were not found to be associated with either antibiotic prescribing or patient recovery.

Comparison to current literature

This study found lower rates of antibiotic prescribing compared to some other observational studies on LRTIs.[23] This is probably because of the inclusion of “acute cough” rather than diagnosis of LRTI. However, we did not find that smokers were more likely to be labelled as having a LRTI compared to non-smokers.

The duration of illness of smokers is similar to other studies, and the finding that smokers do not recovery any more slowly than non-smokers is consistent.[9] Antibiotic prescribing was not associated with any extra benefit to smokers with acute cough, which is in agreement with the conclusions of a review looking at antibiotic prescribing for acute bronchitis in smokers.[18]

Our study confirmed clinicians perceive antibiotics are more beneficial to smokers,[2] and that clinicians are more likely to prescribe antibiotics for smokers.[4] Clinicians are more likely to prescribe antibiotics if a patient expects them.[24] [25] In our study, smokers more than non-smokers believed antibiotics would help them if cough lasted more than a few days.

Our study found that smokers believe that antibiotics are indicated for their cough if it lasts longer than a few days, confirming previous studies. [26] There is a strong association between patients wanting antibiotics and antibiotics being prescribed

them, [26] so this may account for some of the noticeable increase in prescriptions for antibiotics for smokers.

Conclusion

Smoking status is an independent factor for antibiotic prescribing in all countries in Europe. However, antibiotic prescribing is not associated with recovery in smokers.

Implications for practice

Smoking status alone should not be a determinant for antibiotic prescribing.

Further Research

This observational study has highlighted that antibiotic prescribing for smokers presenting with acute cough is higher than non-smokers tin primary care in Europe. To our knowledge, no double-blind randomised controlled trial of antibiotic prescribing in smokers with acute cough has been conducted.

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Box 1: Smoking Status Categories

Smoking Status	Definition
Smoker	Smoked >100 cigarettes in lifetime AND still smoking OR given up < 1year
Ex-Smoker	Smoked >100 cigarettes in lifetime AND given up ≥ 1 year
Non-Smoker	Never smoked or had smoked <100 cigarettes in lifetime

Figure 1: Participant Flow Chart

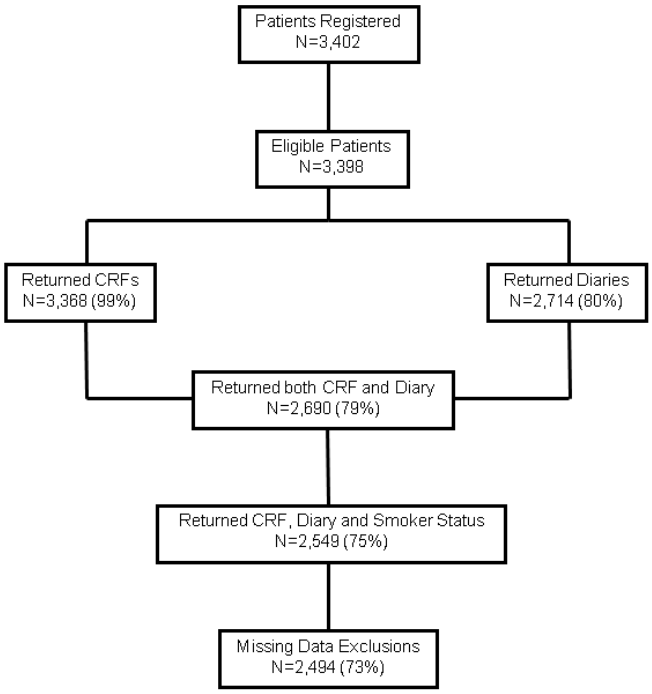

Figure 2: Average clinician-rated symptom severity scores split by smoking category
(Average clinician rated symptom severity scores are plotted for each smoking status category and for each symptom, with error bars inflated for clinician-level clustering)

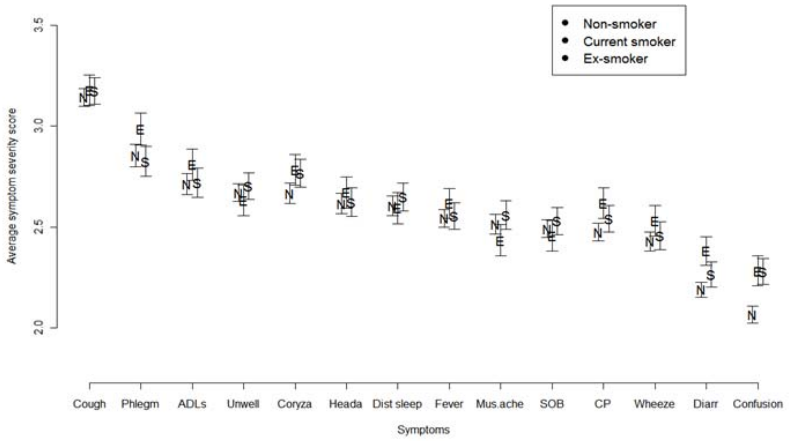

Figure 3: Prescribed antibiotics by network and smoker status