Respiratory Medications and the Risk of Cardiac Arrhythmias

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Background: Medications used to treat respiratory diseases include beta-adrenoceptors, antimuscarinics, inhaled and oral corticosteroids, and theophyllines. Most of these drugs have been associated indirectly with cardiac rhythm disorders, but epidemiologic evidence is limited.

Methods: To evaluate the association between respiratory drugs and the occurrence of rhythm disorders among patients with asthma and those with chronic obstructive pulmonary disease, we conducted a case–control study nested in a population-based cohort of individuals 10–79 years of age and registered in the U.K. General Practice Research Database after 1 January 1994. The analysis included 710 confirmed cases and 5000 controls frequency-matched to cases by age (interval of 1 year) and sex.

Results: No increased risk of arrhythmias overall was found among users of inhaled steroids (relative risk = 1.0; 95% confidence interval = 0.8–1.3). Short-term use of theophylline was weakly associated with arrhythmia (1.8; 1.0–3.3). An increased risk was found among users of oral steroids, and the relative risk was greater at the beginning of therapy (2.6; 2.0–3.5). The risk of atrial fibrillation was increased, especially for short-term use of oral steroids (2.7; 1.9–3.8), and a weak association was seen for theophyllines, especially short-term use (1.8; 0.9–3.7). Supraventricular tachycardia was associated with long-term use of oral steroids (2.1; 0.8–5.7), long-term use of antimuscarinics (1.7; 0.7–4.1), and short-term use of theophylline (4.0; 0.9–18.1). Ventricular arrhythmias were associated with oral steroids (3.2; 0.8–13.3) and beta-adrenoceptors (7.1; 0.8–65.9).

Conclusions: Oral steroids and theophylline were the therapeutic groups associated with risk of developing atrial fibrillation, especially with new courses of therapy. Results from this study also are consistent with certain suspected dysrhythmic effects of theophyllines, with supraventricular tachycardia associated with antimuscarinics, and with ventricular arrhythmias associated with beta-adrenoceptors.

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Asthma and chronic obstructive pulmonary disease (COPD) are common chronic conditions, especially in the elderly. According to the 1993 National Health Survey in the United States, the prevalence of asthma in persons 65 years and older was 4.8%, and the prevalence of COPD was 6.2%.[1] Medications used to treat these respiratory diseases include beta-adrenoceptors, antimuscarinics, inhaled and oral corticosteroids, and theophyllines. Most of these drugs have been associated either directly or indirectly with rhythm disorders.[2–10] The nature of these relations and their clinical consequences are uncertain.

We used the General Practice Research Database in the United Kingdom to assess the role of respiratory drugs on the occurrence of rhythm disorders among patients with asthma and those with COPD.

METHODS

Source Population

The General Practice Research Database contains computerized medical information entered systematically by general practitioners and sent anonymously to the Medicines and Healthcare Products Regulatory Agency.[11] Data are recorded and sent anonymously to the Agency, which then organizes this information for research use. The recorded information includes demographic data, medical diagnoses from general practitioners visits, specialists' referrals and hospitalizations, laboratory tests results, all prescriptions issued, and a free text section. When a patient's prescription is written, it is computer-generated and recorded on the patient's computerized file. An additional requirement is recording of the indication for new courses of therapy.

Multiple studies and reviews have been published describing this database in detail and documenting the com-

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pleteness and validity of the information recorded by the general practitioners.[11,12] Over 90% of all referrals are entered into general practitioners' computers with a code that reflects the specialist's diagnosis.[13] Recent studies have also confirmed the validity of using the General Practice Research Database for epidemiologic research regarding arrhythmias in association with specific drugs.[14,15]

Study Cohort

From the source population, which includes approximately 3 million individuals permanently registered with a general practitioner, we identified all patients 10–79 years old on 1 January 1994 who had at least 2 years' enrollment with the general practitioner and a previous diagnosis of asthma or COPD. Patients were classified according to a recorded diagnosis of asthma only, COPD only, or both asthma and COPD. One of our eligibility criteria was that patients had to be free of cancer at start date to avoid the many serious complications of cancer and its treatment. The final study cohort consisted of 116,094 individuals. All study members were followed up from a start date of 2 January 1994, until the earliest of the following study end points: a code suggesting cardiac arrhythmia, cancer diagnosis or death, or December 2000. The study protocol was approved by the General Practice Research Database Scientific Ethical and Advisory Group (SEAG).

Case Ascertainment and Validation

We identified 1714 individuals with a diagnostic code indicating a cardiac rhythm disorder. (Codes are listed in an appendix, available with the electronic version of this article.) Patients were defined as cases of arrhythmias when the diagnosis was confirmed by a specialist. We classified cases into the following subgroups: 1) sinus arrhythmias, 2) atrial arrhythmias (atrial flutter and atrial fibrillation), 3) atrioventricular node tachycardias (supraventricular tachycardia), 4) ventricular arrhythmias (ventricular fibrillation and ventricular tachycardia), 5) atrial or ventricular ectopic beats, and 6) arrhythmias not specified otherwise To allow for blinded revision of the patient profiles, all patient personal identifiers were suppressed and information on relevant drug exposure was removed. We reviewed automated patient profiles to exclude those patients not referred to a consultant or admitted to hospital. Finally, we requested from the general practitioners clinical records for all 1126 potential cases, and we received valid information for 1064 patients (94%). Patient confidentiality was always maintained.

After review of all available information, 354 patients were not considered cases of cardiac arrhythmias for the following reason: diagnosis not confirmed by a specialist (n = 214), chronic atrial fibrillation (n = 46), acute myocardial infarction or angina in the month prior (n = 45), arrhythmias developed in the hospital (n = 15), other cardiac diagnoses (n = 15), cancer recorded within 90 days after the index date (n = 8), date of first diagnosis unknown (n = 6), and congenital defects or hereditary arrhythmias (n = 5). The remaining 710 cases were considered cases of cardiac arrhythmia. Of these, 108 (15%) cases had a documented history of arrhythmia. The date of arrhythmia among the cases was their index date.

We sampled 5000 controls from the study cohort, frequency-matched to cases by age (within 1 year) and sex. In selecting controls, an index date was randomly assigned to each individual from their eligible person-time so that the likelihood of being selected as a control was proportional to their person-time at risk.

Exposure Definition

We defined 3 time-windows of exposure for individual respiratory drugs: nonuse, current use, and past use. Current use referred to use that lasted until the index date or ended in the month before the index date based on the length of drug therapy as prescribed by the general practitioner. Past use ended between 31 days and 1 year before the index date. Finally, nonusers were defined as patients who did not receive drug treatment during the year before the index date. Duration of therapy was defined as the period corresponding to consecutive prescriptions (less than 2-month interval between 2 prescriptions). We classified users into short-term when treatment duration was up to 3 months and long-term when this was greater than 3 months. The same time-windows were used for all drugs included in the analysis.

Analysis

We computed incidence rates (IRs) of arrhythmias and 95% confidence intervals (CIs) using the number of cases as the numerator and the total number of person-years as denominator. Incidence rates were also calculated within strata of age and sex. We performed a nested case–control analysis to better estimate the effects of respiratory drugs, as well as the contribution of other potential risk factors such as use of other medications (nonsteroidal antiinflammatory drugs, aspirin, paracetamol, antihistamines, cisapride, antipsychotics, antidepressants, antibiotics, and antihypertensives) and comorbidity (cardiovascular diseases, hyperthyroidism, and diabetes). To further distinguish effects of certain medications from the conditions for which the medications are used, we also identified and controlled for exacerbations of the underlying illness during the past year, as indicated by hospitalizations, general practitioner or outpatients visits. The date of arrhythmia among the cases was their index date.

We use unconditional logistic regression to compute adjusted estimates of relative risk (RR) of arrhythmia and 95% CI associated with use of individual respiratory drugs compared with nonuse. Age, sex, calendar year, smoking, alcohol, body mass index (BMI), recent exacerbations, history of rhythm disorders, use of other drugs, and comorbidi-

ties were introduced in the model to control for potential confounding. Analyses were performed for total arrhythmias as well as according to specific types of arrhythmia (atrial fibrillation, ventricular arrhythmia, and supraventricular tachycardia).

RESULTS

The incidence rate of any arrhythmia was 2.2 per 1000 person-years. The most commonly reported arrhythmia was atrial fibrillation in 468 cases, followed by 77 cases of ectopic beats, 72 cases of supraventricular tachycardia, 51 cases of atrial flutter, 36 cases of sinus arrhythmia, and 20 cases of ventricular arrhythmias; in 14 cases, the type of arrhythmia was not specified. Thirty patients were diagnosed with more than 1 type of arrhythmia. The incidence of an episode of atrial fibrillation was 1.4 per 1000 person-years. Figure 1 shows incidence rates for any cardiac arrhythmia, atrial fibrillation, and supraventricular tachycardia. Men were at higher risk of any arrhythmia and atrial fibrillation, whereas women had a higher risk of supraventricular tachycardia (data not shown).

We found an increased risk of arrhythmias for persons with cardiovascular disease (1.6; 1.3–2.0) and hyperthyroidism (2.2; 1.1–3.9) (Table 1). Valvular heart disease was strongly associated with arrhythmia (4.5; 3.1–6.7). No association was observed with alcohol, diabetes, or hypertension. We found no increased risk of arrhythmia among patients with a diagnosis of COPD only, and among patients with both COPD and asthma compared with patients who had asthma only. Nonrespiratory medications that were associated to some degree with arrhythmia included cisapride (2.3; 0.7–7.6), antipsychotics (1.4; 0.9–2.3), antibiotics (1.6; 1.2–2.0), and antihypertensives (1.6; 1.3–2.0). All therapeutic subgroups of antihypertensives presented a similar risk (data not shown).

Table 2 presents the association of respiratory drugs with the development of any cardiac arrhythmias. Users of oral steroids had more than a 2-fold increased risk compared with nonusers, with greater risk at the beginning of therapy (2.6; 2.0–3.5). No increased risk was found among users of inhaled steroids (1.0; 0.8–1.3) or in users of beta-adrenoceptors (0.9; 0.7–1.2). We examined the effect among individual beta agonists, and found that none was a risk factor for the occurrence of cardiac arrhythmias (data not shown). Short-term use of theophylline was weakly associated with arrhythmia (1.8; 1.0–3.3). No other respiratory drugs presented an increased risk of arrhythmia. No increased risk was found among users of multiple respiratory drugs (1.0; 0.8–1.3) (data not shown). The estimates did not change substantially after adjustment for other potential confounding factors.

Table 3 shows the association of respiratory drugs with specific types of arrhythmia. An increased risk of atrial fibrillation was seen for oral steroids, especially with short-term use (2.7; 1.9–3.8). A weak association was seen for theophyllines, especially short-term use (1.8; 0.9–3.7). Supraventricular tachycardia was associated with long-term use of oral steroids (2.1; 0.8–5.7), long-term use of antimuscarinics (1.7; 0.7–4.1), and short-term use of theophylline (4.0; 0.9–18.1) (Table 3). Respiratory drugs associated with ventricular arrhythmias included oral steroids (3.9; 1.2–13) and beta-adrenoceptors (7.1; 0.8–65.9). When past users were included with nonusers in the reference group to enhance stability, the strongest association with ventricular arrhythmias remained in long-term use of beta-adrenoceptors (4.7; 1.0–22.1).

Stratification by history of arrhythmia did not change overall results (data not shown). The RR associated with oral steroids use was 1.9 (0.8–4.6) among patients with a history of arrhythmias and 2.1 (1.6–2.7) among cases without a history of arrhythmias. The RR associated with beta-adrenoceptor use was 1.2 (0.5–2.6) and 0.9 (0.6–1.1), respectively, for patients with and without such a history.

DISCUSSION

The incidence of atrial fibrillation reported in various studies ranges from 0.5 to 19.2 per 1000 person-years and increases with age.[16,17] In our study, the incidence was 1.4

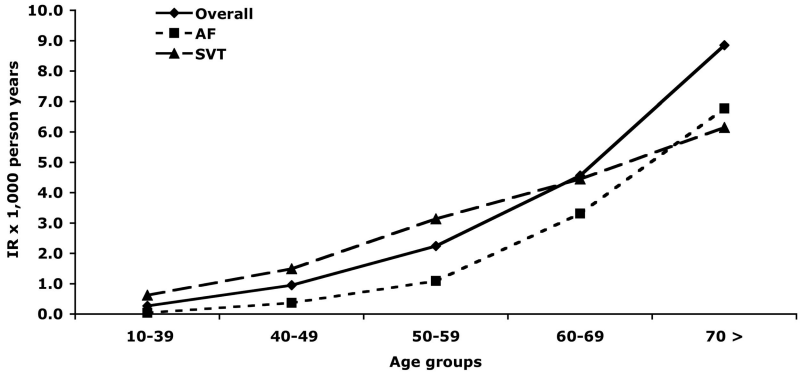

FIGURE 1. Incidence rate of cardiac arrhythmias.

TABLE 1. Risk Factors for Rhythm Disorders Among Cases and Controls

	Cases (n = 710) %	Controls (n = 5000) %
Sex		
Male	49.7	49.5
Female	50.3	50.5
Age (years)		
10–49	11.4	11.7
50–59	13.1	16.3
60–69	28.9	28.7
70–79	46.6	43.3
Smoking		
Nonsmoker	56.9	52.1
Smoker	19.3	25.6
Exsmoker	15.2	14.5
Unknown	8.6	7.8
Body mass index (kg/m^2)		
20–24	25.9	29.2
<20	4.8	5.7
35–60	49.6	45.5
Unknown	19.7	19.6
Alcohol (units)		
Nonuser	37.3	36.1
<20	33.0	35.0
≥20	8.9	8.2
Unknown	20.8	20.7
Cardiovascular diseases*		
No	46.9	64.5
Yes	53.1	35.5
Hypertension		
No	66.5	76.5
Yes	33.5	23.5
Hyperthyroidism		
No	97.9	99.0
Yes	2.1	1.0
Diabetes		
No	93.2	94.8
Yes	6.8	5.2
Asthma/COPD		
Asthma only	50.1	53.2
COPD only	22.7	19.3
Asthma and COPD	27.2	27.4
Exacerbation of asthma/COPD in the last year		
No	83.4	89.2
Yes	16.6	10.8
History of rhythm disorders		
No	84.8	96.3
Yes	15.2	3.7

*Includes myocardial infarction, angina, heart failure, valvular disease, cardiac surgery, and other cardiovascular diseases.

per 1000 person-years, and the highest incidence was observed in elderly men.

The associations for traditional risk factors of arrhythmia that we observed in our study are in line with previous studies in atrial fibrillation.[16,17] Among cardiovascular diseases, the risk associated with valvular diseases was the greatest. We also found an increased risk with hyperthyroidism, a recognized risk factor for the development of supraventricular tachycardia.[18,19] In our study, diabetes and hypertension were not associated with arrhythmias after adjustment for cardiovascular disease. When comparing these results with results of previous studies, one should note the majority of these other studies included only ventricular or "serious" cardiac arrhythmias.

Among users of respiratory medications, oral steroids and theophylline were the therapeutic groups associated with an increased risk of developing cardiac arrhythmias, especially with new courses of therapy. Both of these associations were mainly the result of higher rates of atrial fibrillation. Theophylline has been associated with arrhythmias,[7] but to our knowledge, oral steroids have not previously been associated with arrhythmias. We considered whether administration of steroids by oral route might be a marker of disease severity, but the association with atrial fibrillation was stronger for oral steroids than for 2 markers of severity (hospitalization for a recent exacerbation or number of prescriptions for beta-adrenoceptors), and controlling for these markers did not explain the association with oral steroids.

Two other notable findings were the association of antimuscarinics with supraventricular tachycardia, and of beta-adrenoceptors with ventricular arrhythmias. Antimuscarinics have been associated previously with supraventricular tachycardia.[8] Of potentially greater clinical significance is the association between beta-adrenoceptors and ventricular arrhythmias. The potential for arrhythmias with beta-adrenoceptors has been recognized.[2,3] Although sufficiently large trials and epidemiologic studies are few, there is some evidence to suggest clinical effects. Suissa et al[20] report an increased risk of acute cardiac death with nebulized and oral beta-adrenoceptors but little if any association with metered-dose inhalers. Bouvy et al[4] found sympathomimetics to be associated with an increased risk of hospitalization for arrhythmia. With regard to myocardial infarction, Suisas et al[21] found only a very weak association with beta-adrenoceptors, but Au et al[22,23] found that new use of beta-adrenoceptors was associated with an increased risk of myocardial infarction and that there was a dose-response between metered dose inhalers and acute coronary syndrome.[23]

It is important to consider several potential limitations of this study and how they may have affected the results. Confounding by disease severity, or indication, is a recognized limitation of nonrandomized studies. The idea that oral corticosteroids have not previously been associated with

TABLE 2. Relative Risk of Rhythm Disorders Associated With use of Respiratory Drugs for Asthma or COPD, According to Recency and Duration*

	Cases (n = 710)	Controls (n = 5000)	Unadjusted RR (95% CI)	Adjusted RR† (95% CI)
Oral steroids				
Nonusers‡	450	3551	1.0	1.0
Current users	144	508	2.2 (1.8–2.8)	2.1 (1.6–2.6)
Short-term	89	248	2.8 (2.2–3.7)	2.6 (2.0–3.5)
Long-term	55	260	1.7 (1.2–2.3)	1.5 (1.1–2.1)
Past users	116	941	1.0 (0.8–1.2)	1.0 (0.8–1.2)
Inhaled steroids				
Nonusers‡	230	1614	1.0	1.0
Current users	351	2280	1.1 (0.9–1.3)	1.0 (0.8–1.3)
Short-term	112	629	1.2 (1.0–1.6)	1.2 (0.9–1.6)
Long-term	239	1651	1.0 (0.8–1.2)	0.9 (0.7–1.2)
Past users	129	1106	0.8 (0.7–1.0)	0.8 (0.6–1.1)
Beta-adrenoceptors				
Nonusers‡	159	1133	1.0	1.0
Current users	392	2563	1.1 (0.9–1.3)	0.9 (0.7–1.2)
Short-term	104	587	1.3 (1.0–1.6)	1.1 (0.8–1.5)
Long-term	288	1976	1.0 (0.8–1.3)	0.8 (0.6–1.1)
Past users	159	1304	0.9 (0.7–1.1)	0.9 (0.7–1.2)
Antimuscarinics				
Nonusers‡	556	3977	1.0	1.0
Current users	109	709	1.1 (0.9–1.4)	0.8 (0.6–1.0)
Short-term	33	157	1.5 (1.0–2.2)	1.2 (0.8–1.8)
Long-term	76	552	1.0 (0.8–1.3)	0.7 (0.5–0.9)
Past users	45	314	1.0 (0.7–1.4)	0.8 (0.6–1.2)
Theophylline				
Nonusers‡	605	4423	1.0	1.0
Current users	80	396	1.5 (1.1–1.9)	1.2 (0.9–1.6)
Short-term	17	52	2.4 (1.4–4.2)	1.8 (1.0–3.3)
Long-term	63	344	1.3 (1.0–1.8)	1.1 (0.8–1.5)
Past users	25	181	1.0 (0.7–1.5)	0.9 (0.6–1.3)
Cromoglycate				
Nonusers‡	697	4939	1.0	1.0
Current users	2	29	0.5 (0.1–2.1)	0.5 (0.1–2.0)
Short-term	0	10	—	—
Long-term	2	19	0.7 (0.2–3.2)	0.6 (0.1–2.9)
Past users	11	32	2.4 (1.2–4.9)	2.8 (1.4–5.8)
Antibiotics				
Nonusers‡	175	1630	1.0	1.0
Current users	202	936	2.0 (1.6–2.5)	1.6 (1.2–2.0)
Short-term	154	664	2.2 (1.7–2.7)	1.7 (1.3–2.2)
Long-term	48	272	1.6 (1.2–2.3)	1.3 (0.9–1.8)
Past users	333	2434	1.3 (1.1–1.5)	1.2 (0.9–1.4)

*Short-term use refers to treatment duration up to 3 mo and long-term to use greater than 3 mo.

†Adjusted for sex, age, calendar year, alcohol use, cardiovascular diseases, hyperthyroidism, diabetes, asthma, and COPD. Also for use of nonsteroidal antiinflammatory drugs, aspirin, oral and inhaled steroids, beta-adrenoceptors, theophylline, antihistamines, antipsychotic drugs, and antihypertensive drugs, and for exacerbation of asthma/COPD in the last year.

‡Reference category.

TABLE 3. Relative Risk of Atrial Fibrillation, Supraventricular Tachycardia, and Ventricular Arrhythmia Associated With Use of Respiratory Drugs for Asthma or COPD, According to Recency and Duration*

	Atrial Fibrillation			Supraventricular Tachycardia			Ventricular Arrhythmia		
	Cases (n = 468)	Unadjusted RR (95% CI)	Adjusted RR† (95% CI)	Cases (n = 72)	Unadjusted RR (95% CI)	Adjusted RR† (95% CI)	Cases (n = 20)	Unadjusted RR (95% CI)	Adjusted RR† (95% CI)
Oral steroids									
Nonusers‡	303	1.0	1.0	53	1.0	1.0	9	1.0	1.0
Current users	97	2.2 (1.7–2.9)	1.9 (1.4–2.6)	9	1.2 (0.6–2.4)	1.6 (0.7–3.7)	6	4.7 (1.7–13.1)	3.9 (1.2–13.0)
Short-term	64	3.0 (2.2–4.1)	2.7 (1.9–3.8)	3	0.8 (0.3–2.6)	1.1 (0.3–3.9)	3	4.8 (1.3–17.7)	3.2 (0.8–13.3)
Long-term	33	1.5 (1.0–2.2)	1.2 (0.8–1.8)	6	1.5 (0.7–3.6)	2.1 (0.8–5.7)	3	4.6 (1.2–16.9)	4.0 (0.9–17.2)
Past users	68	0.8 (0.6–1.1)	0.8 (0.6–1.1)	10	0.7 (0.4–1.4)	0.8 (0.4–1.8)	5	2.1 (0.7–6.3)	1.8 (0.6–6.0)
Inhaled steroids									
Nonusers‡	155	1.0	1.0	28	1.0	1.0	5	1.0	1.0
Current users	234	1.1 (0.9–1.3)	1.0 (0.7–1.3)	30	0.8 (0.5–1.3)	0.9 (0.5–1.9)	14	2.0 (0.7–5.5)	0.7 (0.2–2.4)
Short-term	82	1.4 (1.0–1.8)	1.4 (1.0–1.9)	5	0.5 (0.2–1.2)	0.5 (0.2–1.5)	2	1.0 (0.2–5.3)	0.3 (0.0–2.0)
Long-term	152	1.0 (0.8–1.2)	0.8 (0.6–1.1)	25	0.9 (0.5–1.5)	1.2 (0.6–2.4)	12	2.3 (0.8–6.7)	0.9 (0.2–3.1)
Past users	79	0.7 (0.6–1.0)	0.8 (0.6–1.1)	14	0.7 (0.4–1.4)	0.8 (0.4–1.8)	1	0.3 (0.0–2.5)	0.2 (0.0–1.9)
Beta-adrenoceptors									
Nonusers‡	106	1.0	1.0	22	1.0	1.0	1	1.0	1.0
Current users	263	1.1 (0.9–1.4)	0.9 (0.7–1.2)	32	2.0 (1.6–2.5)	0.7 (0.3–1.4)	17	7.5 (1–56.5)	7.1 (0.8–65.9)
Short-term	73	1.3 (1.0–1.8)	1.2 (0.9–1.7)	7	0.6 (0.3–1.4)	0.6 (0.2–1.6)	2	3.9 (0.3–42.7)	4.5 (0.4–55.5)
Long-term	190	1.0 (0.8–1.3)	0.8 (0.5–1.1)	25	0.7 (0.4–1.2)	0.7 (0.3–1.6)	15	8.6 (1.1–65.2)	8.8 (0.9–85.5)
Past users	99	0.8 (0.6–1.1)	0.9 (0.6–1.2)	18	0.7 (0.4–1.3)	0.8 (0.4–1.5)	2	1.7 (0.2–19.2)	2.8 (0.2–33.3)
Antimuscarinics									
Nonusers‡	363	1.0	1.0	58	1.0	1.0	15	1.0	1.0
Current users	77	1.2 (0.9–1.5)	0.7 (0.5–1.0)	10	1.0 (0.5–1.9)	1.5 (0.7–3.4)	4	1.5 (0.5–4.5)	0.8 (0.2–2.7)
Short-term	26	1.8 (1.2–2.8)	1.3 (0.8–2.1)	2	0.9 (0.2–3.6)	1.1 (0.3–5.0)	0	—	—
Long-term	51	1.0 (0.7–1.4)	0.6 (0.4–0.8)	8	1.0 (0.5–2.1)	1.7 (0.7–4.1)	4	1.9 (0.6–5.8)	1.0 (0.3–3.6)
Past users	28	1.0 (0.7–1.5)	0.7 (0.5–1.1)	4	0.9 (0.3–2.4)	1.2 (0.4–3.5)	1	0.8 (0.1–6.4)	0.7 (0.1–6.2)
Theophylline									
Nonusers‡	389	1.0	1.0	67	1.0	1.0	18	1.0	1.0
Current users	61	1.8 (1.3–2.3)	1.4 (1.0–1.9)	3	0.5 (0.2–1.6)	0.6 (0.2–2.1)	2	1.2 (0.3–5.4)	0.6 (0.1–2.7)
Short-term	11	2.4 (1.2–4.6)	1.8 (0.9–3.7)	2	2.5 (0.6–10.6)	4.0 (0.9–18.1)	0	—	—
Long-term	50	1.7 (1.2–2.3)	1.3 (0.9–1.8)	1	0.2 (0.0–1.4)	0.2 (0.0–1.8)	2	1.4 (0.3–6.2)	0.8 (0.2–3.6)
Past users	18	1.1 (0.7–1.9)	0.9 (0.5–1.5)	2	0.7 (0.2–3.0)	0.9 (0.2–3.9)	0	—	—
Antibiotics									
Nonusers‡	121	1.0	1.0	20	1.0	1.0	1		1.0
Current users	136	2.0 (1.5–2.5)	1.5 (1.1–2.0)	22	1.9 (1.0–3.5)	2.1 (1.1–4.1)	5	8.7 (11.0–74.7)	5.0 (0.5–46.8)
Short-term	108	2.2 (1.7–2.9)	1.7 (1.3–2.3)	15	1.8 (0.9–3.6)	2.0 (1.0–4.2)	5	12.3 (1.4–105.3)	7.0 (0.7–66.5)
Long-term	28	1.4 (0.9–2.1)	1.0 (0.6–1.6)	7	2.1 (0.9–5.0)	2.3 (0.9–6.0)	0	—	—
Past users	211	1.2 (0.9–1.5)	1.1 (0.8–1.4)	30	1.0 (0.6–1.8)	1.1 (0.6–2.0)	14	9.4 (1.2–71.4)	7.5 (0.9–60.0)

*Short-term use refers to treatment duration up to 3 mo and long-term to use greater than 3 mo.

†Adjusted for sex, age, calendar year, alcohol use, cardiovascular diseases, hyperthyroidism, diabetes, asthma, COPD, NSAIDs, aspirin, oral and inhaled steroids, beta-adrenoceptors, theophylline, antihistamines, antipsychotics, antihypertensive use, and exacerbation of Asthma/COPD in the last year.

‡Reference category.

arrhythmias lends some caution to the interpretation of this finding, and we would stress the need for additional studies assessing this possible association. In general, the results for specific types of arrhythmias show different patterns than the overall results and deserve closer consideration.

First is the possibility that general practitioners would tend not to prescribe selective beta-adrenoceptors in patients considered to be at higher risk of ventricular arrhythmia. We minimized this possibility by adjusting our analyses for the presence of a wide variety of diseases such as ischemic heart disease and congestive heart failure. In addition, beta-adrenoceptors and oral corticosteroids are highly correlated with exacerbations that, themselves, may lead to hypoxemia and, possibly, cardiac arrhythmias. Hospitalizations, general practitioner and outpatient visits for exacerbations, however, were associated with arrhythmias less strongly than these medications. Hence, controlling for exacerbations did not explain the associations with the medications. Exacerbations in the past year includes patients with current exacerbations (eg, in the past week) along with more distant exacerbations. With regard

to acute effects of exacerbation, the measure used here is less accurate and allows for residual confounding. Nevertheless, controlling for exacerbations in the past year would also remove some of the possible effect of acute exacerbations, and there was no indication that controlling for exacerbations in the past year had any impact on the results. Nevertheless, further studies are needed to better distinguish the acute effects of medications and exacerbations on arrhythmias.

Despite these limitations, results from this study also are consistent with certain suspected dysrhythmic effects of theophyllines, supraventricular tachycardia associated with antimuscarinics, and ventricular arrhythmias associated with beta-adrenoceptors. In addition, we report here an association of oral steroids with several types of arrhythmia. Of these arrhythmias, atrial fibrillation affected the greatest number of patients, but ventricular arrhythmias may be the most serious of the disorders.

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