ORIGINAL ARTICLE

Cardiovascular medication use in patients with undiagnosed obstructive sleep apnoea

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Background: A study was undertaken in patients with undiagnosed sleep apnoea/hypopnoea syndrome (OSAS) to document the use of prescribed medications, especially those used in cardiovascular diseases, in the year before the OSAS diagnosis was confirmed.

Methods: A total of 549 patients with OSAS (401 men of mean age 47.2 years, mean body mass index (BMI) 35.5 kg/m², mean apnoea/hypopnoea index (AHI) 47.2 and 148 women of mean age 50.2 years, BMI 39.6 kg/m², AHI 32.6) were each matched to one general population control by age, sex, geographical location, and family physician. Medication use was evaluated for patients and controls using a database containing information about all prescriptions completed in the province of Manitoba, Canada.

Results: In the year before OSAS was diagnosed, prescribed medication costs were \$155.91 (Can) (95% CI \$91.34 to \$220.49) greater for cases than for controls. Cases were dispensed 3.3 (95% CI 1.5 to 5.2) more prescriptions, were on 1.2 (95% CI 0.8 to 1.6) more medications, and were supplied with 157.4 (95% CI 95.9 to 218.8) more daily doses of medication. The odds ratio of OSAS cases being on a prescribed medication was 1.88 relative to controls (95% CI 1.38 to 2.54, $p < 0.0001$). In the same year 36.6% of cases and 19.7% of controls were using medications for cardiovascular disease (OR 2.82, 95% CI 2.05 to 3.89, $p < 0.0001$), consuming 79.4 (95% CI 48.9 to 109.8) more daily doses of medication, having been dispensed 1.7 (95% CI 1.0 to 2.4) more prescriptions, and at a \$75.26 (95% CI \$44.03 to \$106.50) greater cost. The odds ratio of patients with OSAS being on medications indicated for the treatment of systemic hypertension was 2.71 (95% CI 1.96 to 3.77) relative to controls; however, such medications might also be prescribed for other indications such as angina pectoris and congestive heart failure, and for the secondary prevention of myocardial infarction. The use of medications indicated for the treatment of systemic hypertension was predicted significantly by age (odds ratio (OR) 1.10 per year), BMI (OR 1.05 per unit), and AHI (OR 1.01 per unit).

Conclusions: In the year before OSAS was diagnosed, patients with OSAS were heavy users of medications, particularly those used to treat cardiovascular diseases.

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Obstructive sleep apnoea/hypopnoea syndrome (OSAS) is a disorder which is characterised by repetitive episodes of apnoeas or hypopnoeas during sleep and the clinical features which occur as a result of the physiological disturbance caused by abnormal breathing events.¹⁻³ The most common symptom in sleep apnoea is excessive daytime sleepiness, which is believed to be caused by repetitive arousals and abnormal sleep architecture caused by the apnoeic episodes.

Systemic arterial blood pressure increases during sleep in patients with sleep apnoea. Increased sympathetic tone is thought to play a role in the nocturnal rise in blood pressure and perhaps in the development of daytime hypertension.⁴⁻⁵ Other factors such as genetics⁶ and abnormal vascular endothelium⁷ may also play a part. Experimental studies in animals⁸ and epidemiological studies in patients with OSAS have linked this disorder to the development of chronic arterial hypertension.⁹⁻¹⁰ The studies that have examined the relationship between sleep apnoea and arterial hypertension suggest that hypertension is 2-3 times more likely in patients with sleep apnoea when confounding variables such as age, sex, and weight are controlled.¹⁰ Other cardiovascular problems including arrhythmias, right sided heart failure, pulmonary hypertension, and nocturnal angina pectoris have also been linked to OSAS.¹¹⁻¹³

Since sleep apnoea is very common, affecting 4% of the male population and 2% of the female population,¹⁴ it has the potential to impact on the use of health care resources. It has

been shown that patients with sleep apnoea are heavy users of health care resources for years before the initial diagnosis of their sleep apnoea.¹⁵ These studies have shown, for example, that physician costs and hospital admissions are increased in this group of patients. The impact of undiagnosed OSAS on medication use is not known. Although drugs used to treat cardiovascular disease are among the most widely prescribed for the general population,¹⁶ we hypothesised that undiagnosed OSAS patients will be even heavier users of these medications than matched controls. Medication use in 549 patients with sleep apnoea for the year before laboratory confirmation of their diagnosis was compared with a matched control group.

METHODS

Selection of patients

All patients first diagnosed with OSAS between 1997 (at least one year after the pharmacy database was established (see below)) and 1999 were included in the study. The diagnosis was confirmed in all patients by polysomnography which included the monitoring of neurophysiological measures (EEG, chin EMG, EOG, anterior tibialis EMG) and cardiorespiratory variables (chest wall motion, abdominal motion, oronasal Pco₂, Spo₂ (by fiberoptic pulse oximeter), and ECG). The key measures obtained from polysomnographic monitoring were apnoea/hypopnoea index (AHI) as one indicator of apnoea severity and time spent

below Sao_2 90% (time <90%) as an index of exposure to hypoxaemia.

Patients who, in addition to sleep apnoea, had another sleep disorder such as co-existing narcolepsy and periodic leg movements which did not resolve on treatment of the apnoea were excluded from the study. Patients whose entire health care services were not paid by the province of Manitoba—for example, those not permanently resident in Manitoba, status Indians, and military personal (whose health care is covered by the Canadian Federal Government)—were also excluded. There remained 551 eligible cases for matching with controls and analysis.

Selection of controls

Each OSAS case was matched with a control subject from the general population for sex, area of residence, postal code, age, and physician. The cases were matched to controls using the Manitoba health population registry and the database which maintains records of physician claims for services and hospital admissions on all residents of Manitoba. As most of the cases had a number of physician contacts before the date they were evaluated in the sleep laboratory, the most frequently seen physician in an ambulatory setting in the previous 2 years was taken as the target for the match. All those who saw the same physician in the same time period as each case were identified. One person was chosen at random for each case if several were available. Of the 551 eligible to be matched with a control, 549 matched at least one person for sex, age within 5 years, and physician (contact with case's most frequent physician). The other two cases had no suitable matches. A 5 year age tolerance was allowed in case a 1 year age match could not be obtained; however, the age difference was chosen so that the control was always older than the case. Of the 549 matches, 546 (99.5%) were exact for age.

This research was designed from the onset to protect confidentiality of cases and controls. Only encrypted forms of subjects' personal health information numbers were used. The study was approved by the University of Manitoba human ethics committee and the access and confidentiality committee of Manitoba Health.

Description of the database

All outpatient prescriptions completed in Manitoba are tracked by the Drug Programs Information Network (DPIN) which was established in 1996.¹⁶ All the dispensing pharmacies in the province of Manitoba are linked in real time with the Manitoba health computer system. Each dispensed prescription generates a record that includes a personal identifier (an encrypted version of the person's health information number), the date the prescription was dispensed, the drug identification number (DIN) of the medication, the dosage prescribed, and the number of doses prescribed. In 1999 this database included 707 specific medications (both generic and brand name) for a total of 3328 products. The personal identifier is used for linking to another database¹⁷ which can then yield region of residence, sex, prescribing physician, and physician claims.

The medications were classified according to the World Health Organization Collaborating Centre for Drug Statistics methodology.¹⁸ This classification divides medications into groups based on organ system or therapeutic class. The classification yields anatomical therapeutic chemical classes (ATC). For example, ATC=C is the group of drugs dispensed for cardiovascular disease. This database does not include prescriptions for hospital inpatients, military personnel, or status Indians. The latter two groups are covered by a different funding source. The database has been validated¹⁶ and 92% of the prescriptions in the database matched the original written prescription. It does not include over the counter medications or products purchased in health food stores.

Primary outcome measures

Information was obtained from the database about all prescriptions dispensed to the cases in the 12 months before the diagnosis of OSAS was first confirmed. For each matched control we obtained information about all their prescriptions for the same time frame as their matched case.

Number of prescriptions

The number of prescriptions and the medication prescribed, classified according to anatomical and therapeutic chemical (ATC) criteria according to WHO methodology,¹⁸ was determined.

Defined daily doses (DDD)

The defined daily dose is the mean dose per day for a medication when used in treating its major indication. The DDD was calculated both for the entire population of cases and controls and for the subgroups of case users and control users (who actually presented the prescriptions). It has been used in quantifying intensity of drug use. Defined daily doses are not available for combination drugs.

Days of drug supplied (DDS)

This is the number of days for which medication is supplied. This value differs from DDD in that, for some indications, different doses of a drug might be prescribed. This measure includes combination drugs for which DDDs are not available.

Cost

The cost in Canadian dollars (\$1Can=\$0.68 US) of medications (per prescription and per year) for the population of cases and controls was calculated.

Predictors of medication use

The following independent variables were evaluated to see whether they significantly impacted on medication use: age, sex, body mass index (BMI), apnoea/hypopnoea index (AHI), percentage time below an Sao_2 of 90% during sleep (time <90%), and Epworth sleepiness scale (ESS), a subjective measure of sleepiness.¹⁹

Statistical methods

Odds ratios comparing drug utilisation among cases and controls were obtained from the Cochran-Mantel-Haenszel test allowing for matching. Paired *t* tests were used to compare cases and controls on continuous variables (days supplied, total cost). Among the cases, logistic regression using stepwise elimination was used to predict drug utilisation as a function of AHI, time below Sao_2 90%, and ESS controlling for age, sex, and BMI. Linear regression was used in a similar way to model the continuous variables. Comparisons between men and women were carried out using unpaired *t* tests. Probability values of <0.05 were considered significant. Confidence intervals were calculated using standard methods and computer programs.^{20,21} Analysis was conducted on a Sun Microsystems work station running SAS version 8.1 (SAS Institute, Cary, North Carolina), and on a PC running Confidence Interval Analysis version 2.03.²¹ When calculating confidence intervals on proportions, the method of Wilson²² was used as recommended.^{20,21}

RESULTS

A total of 549 cases (401 men) with OSAS and matched controls were eligible for analysis. Their demographic characteristics are shown in table 1. The patients were, on average, middle aged; the men were significantly younger with a significantly lower BMI but higher AHI than the women.

Table 1 Mean (SD) characteristics of study patients

	Men (n=401)	Women (n=148)	Difference (95% CI)	p value*
Age (years)	47.2 (11.3)	50.2 (11.4)	-3.1 (-5.2 to -0.9)	0.0051
BMI (kg/m ²)	35.5 (7.5)	39.6 (10.0)	-4.1 (-5.6 to -2.5)	<0.0001
AHI (events/h)	47.2 (32.0)	32.6 (30.0)	14.5 (8.6 to 20.5)	<0.0001
Time<90%	19.2 (21.6)	16.0 (24.8)	3.1 (-1.1 to 7.4)	0.1731
ESS	13.0 (5.7)	12.5 (5.9)	0.6 (-0.5 to 1.7)	0.2899

BMI = body mass index; AHI = apnoea/hypopnoea index; ESS = Epworth sleepiness scale score; Time <90% = percentage of time below an SaO₂ of 90%. *Unpaired *t* test.

Table 2 Difference in use of medication per year between OSAS cases and controls

	Total (n=549)		Men (n=401)		Women (n=148)	
	Cases	Difference (95% CI)	Cases	Difference (95% CI)	Cases	Difference (95% CI)
Number of drugs used	3.8	1.2 (0.8 to 1.6)	3.2	0.9 (0.5 to 1.3)	5.5	2.0 (1.2 to 2.9)
DDD	366.6	99.4 (3.7 to 195.2)	286.4	100.2 (46.1 to 154.4)	583.8	97.2 (-229.1 to 423.5)
DDS	444.8	157.4 (95.9 to 218.8)	345.7	108.1 (47.3 to 168.8)	713.1	290.9 (133.5 to 448.3)
Prescriptions per year	11.8	3.3 (1.5 to 5.2)	9.1	2.0 (0.3 to 3.8)	18.8	6.9 (1.8 to 12.0)
Total cost per year (\$Can)	407.98	155.91 (91.34 to 220.49)	324.29	108.73 (44.25 to 173.22)	634.74	283.73 (120.05 to 447.42)
Cost per prescription (\$Can)	34.72	2.51 (-0.86 to 5.87)	35.52	2.29 (-2.25 to 6.84)	33.69	2.91 (-1.74 to 7.57)

DDD = defined daily dose; DDS = days of drug supplied. Difference=mean difference (95% CI) between cases and controls.

Table 3 Difference in use of cardiovascular medications per year between OSAS cases and controls

	Total (n=549)		Men (n=401)		Women (n=148)	
	Cases	Difference (95% CI)	Cases	Difference (95% CI)	Cases	Difference (95% CI)
DDD	158.5	73.9 (41.0 to 106.9)	140.5	60.5 (24.8 to 96.2)	207.5	110.4 (35.2 to 185.6)
DDS	169.3	79.4 (48.9 to 109.8)	154.2	69.5 (35.3 to 103.6)	210.3	106.2 (40.6 to 171.7)
Prescriptions per year	3.5	1.7 (1.0 to 2.4)	3.2	1.5 (0.8 to 2.3)	4.4	2.2 (0.7 to 3.8)
Total cost per year (\$Can)	154.96	75.26 (44.03 to 106.50)	145.27	68.38 (32.98 to 103.79)	181.22	93.89 (28.30 to 159.49)
Cost per prescription (\$Can)	44.27	3.48 (-7.88 to 14.86)	45.83	7.58 (-8.62 to 23.78)	41.09	-4.09 (-17.73 to 9.55)

DDD = defined daily dose; DDS = days of drug supplied. Difference=mean difference (95% CI) between cases and controls.

Use of all drugs

From the drug database we analysed all prescriptions dispensed to patients and their controls. At least one prescribed medication was used by 10.2% (95% CI 5.4 to 15.0; *p*<0.0001) more cases (83.4%) than controls (73.2%) in the 1 year under consideration. Male cases (80%) were more likely to have been prescribed at least one medication than controls (68.3%), the difference being 11.7% (95% CI 5.7 to 17.7; *p*=0.0001). However, the difference between female cases (92.6%) and controls (86.5%) of being prescribed at least one medication was 6.1% (95% CI -1.0 to 13.3; *p*=0.09) and did not reach significance.

Different measures of intensity of use per person per year were calculated. Table 2 shows that cases were on more medications, had more prescriptions per year, and had higher DDD and DDS. Furthermore, the total cost of medications was higher in cases than in controls. However, there was no difference between cases and controls in the cost per prescription. The differences between cases and controls were in the same directions for both men and women; for number of drugs (*p*=0.02) and DDS (*p*=0.03) the differences were significant, but for the other measures of intensity there was no significant difference in magnitude.

Female cases (92.6%) were more likely to be using at least some medication than male cases (80.1%); the difference (12.5%, 95% CI 6.0 to 17.8; *p*<0.0001) was statistically significant. Table 2 shows that female cases had 367.4 more DDS than male cases (713.1 *v* 345.7, *p*<0.0001). The total cost of medications for female cases was \$310.45 more than for males (\$634.7 *v* \$324.3, *p*<0.0001). The cost of medications for female controls was also higher than for male controls.

Use of cardiovascular system drugs

From all drugs we focused on the medications normally used to treat cardiovascular disease (see table 3 and box 1). At least one cardiovascular medication prescription was completed by 16.9% (95% CI 12.1 to 21.7; *p*<0.0001) more cases (36.6%) than controls (19.7%) in the 1 year under review. Male cases (34.7%) were more likely to have been prescribed at least one cardiovascular medication than controls (18.2%), the difference being 16.5% (95% CI 10.9 to 21.9; *p*<0.0001). Female cases (41.9%) were more likely to have been prescribed at least one cardiovascular medication than controls (23.7%), with a difference of 18.2% (95% CI 8.4 to 27.6; *p*<0.0001).

Different measures of intensity of cardiovascular drug use per person per year were calculated. Table 3 shows that cases were on more medications, had more prescriptions per year, and had higher DDD and DDS. Furthermore, the total cost of medications was higher in cases than in controls. However, there was no difference between cases and controls in the cost per prescription. The differences between cases and controls were in the same directions for both men and women and there was no significant difference in magnitude.

Female cases (41.9%) were not more likely to use cardiovascular medications than male cases (34.7%); the difference (7.2%, 95% CI -1.8 to 16.5; *p*=0.126) was not significant. There was no significant difference between men and women for drug use, DDS, and total cost of cardiovascular drugs.

Because the ATC=C category includes many drug classes, we divided them into three large groups based on the way they

Box 1 Drugs used in cardiovascular disease

Antihypertensive drugs

- Anti-adrenergic agents, centrally acting: methyl dopa (levorotatory), methyl dopa (racemic), clonidine
- Anti-adrenergic agents, peripherally acting: doxazosin, prazosin, terazosin
- Agents acting on arteriolar smooth muscle: hydralazine, minoxidil
- Diuretics: amiloride, chlorthalidone, hydrochlorothiazide, indapamide, metolazone, spironolactone, triamterene, hydrochlorothiazide, potassium
- Loop diuretics: furosemide
- Beta blocking agents: acebutolol, atenolol, labetalol, metoprolol, nadolol, pindolol, propranolol, sotalol, timolol
- Beta blocking agents and other diuretics: atenolol and other diuretics, pindolol and other diuretics
- Selective calcium channel blocker with mainly vascular effect: amlodipine, felodipine, nifedipine
- ACE inhibitors, plain: benazepril, captopril, cilazapril, enalapril, fosinopril, lisinopril, perindopril, quinapril, ramipril
- ACE inhibitors, combinations: lisinopril and diuretics
- Angiotensin II antagonists, plain: candesartan, irbesartan, losartan
- Angiotensin II antagonists, combinations: losartan and diuretics

Cholesterol and triglyceride reducers

- Atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, simvastatin, gemfibrozil, fenofibrate, cholestyramine, nicotinic acid

Other cardiovascular drugs

- Cardiac glycosides: digoxin
- Antiarrhythmics, class I and III: aminodarone, disopyramide, propafenone, quinidine
- Cardiac stimulants excluding cardiac glycosides: epinephrine, epinephrine combinations
- Vasodilators used in cardiovascular diseases: glyceryl trinitrate, isosorbide dinitrate
- Selective calcium channel blockers with direct cardiac effect: diltiazem, verapamil

are usually used clinically: drugs that reduce blood pressure, drugs that lower lipids, and drugs whose main effect is on the heart or the coronary circulation (box 1). We first examined drugs that are approved and most widely used to lower systemic arterial blood pressure (antihypertensives) in Canada. Clinicians might use these medications not just for controlling high blood pressure, but also for other indications and benefits from reducing blood pressure such as for the treatment of angina pectoris, congestive heart failure, and the secondary prevention of myocardial infarction in high risk patients. There is no way to determine from the database the specific indication for which a drug is prescribed. Antihypertensive drugs were far more likely to be prescribed for cases than for controls (31.7% v 16.4%, $p < 0.0001$). The odds ratio

Figure 1 Effect of Epworth sleepiness scale on the predicted probability and 95% confidence band for any medication use for a 45 year old man with OSAS. The more sleepy the patient, the higher the probability of drug use.

for OSAS patients using antihypertensive agents compared with controls was 2.71 (95% CI 1.96 to 3.77). The cases had a mean of 61.6 more DDS for antihypertensive drugs (126.9 v 65.3, $p < 0.0001$) and spent an average of \$47.88 more on antihypertensive drugs than controls (\$95.88 v \$48.00, $p < 0.0001$). We then calculated the intensity of drug use for each antihypertensive drug category including anti-adrenergic drugs, diuretics, loop diuretics, beta blockers, calcium channel blockers, and angiotensin converting enzyme (ACE) inhibitors. Table 4 shows that cases had significantly more DDS on diuretics, calcium channel blockers, and ACE inhibitors and spent significantly more on diuretics, beta blockers, calcium channel blockers, and ACE inhibitors than controls.

We also estimated the differences in antihypertensive drug use for men and women. At least one antihypertensive drug was prescribed to 28.7% of the male cases and 14.7% of the male controls (OR 2.65, 95% CI 1.78 to 3.93, $p < 0.0001$). Antihypertensives were prescribed to 39.9% of the female cases and 20.9% of the female controls (OR 2.87, 95% CI 1.59 to 5.16, $p = 0.0002$). We calculated the relative likelihood of female cases versus male cases having a prescription for each antihypertensive drug, other cardiovascular drugs, and cholesterol and triglyceride reducers. Women were more likely to be dispensed prescriptions for diuretics and ACE inhibitors than men (RR 2.37, 95% CI 1.48 to 3.80, $p = 0.0003$; RR 1.60, 95% CI 1.11 to 2.31, $p = 0.0131$, respectively).

Predicting probability of drug use in OSAS patients

In order to determine whether any of the measured independent variables (age, BMI, AHI, time <90%, ESS) might predict the use of drugs for patients with OSAS, a logistic regression analysis was used with stepwise elimination. The results are summarised in table 5. Medication use could generally be predicted by age, sex, and ESS. The relationship between drug use and ESS is shown in fig 1. Cardiovascular drug use was predicted by age, BMI, and time <90%. Age, BMI,

Table 4 Difference in intensity of drug use between OSAS cases and controls for cardiovascular medications

	ΔDDS mean	95% CI	p value	ΔTotal cost (\$Can)	95% CI	p value
Anti-adrenergic drugs	3.6	-1.0 to 8.2	0.1264	4.65	-0.20 to 9.50	0.0600
Diuretics	14.1	6.0 to 22.3	0.0007	2.36	0.42 to 4.29	0.0171
Loop diuretics	6.0	-0.5 to 12.6	0.0713	1.02	0.13 to 1.92	0.0254
Beta blockers	6.9	-1.2 to 15.0	0.0927	5.09	0.42 to 9.77	0.0328
Calcium channel blockers	16.1	6.8 to 25.5	0.0008	24.16	11.49 to 36.83	0.0002
ACE-I	22.2	11.4 to 32.9	<0.0001	22.85	9.55 to 36.15	0.0008
OCD	6.4	-2.2 to 15.1	0.1440	4.43	-1.93 to 10.78	0.1719
Cholesterol and triglyceride reducers	3.9	-3.3 to 11.2	0.2842	10.70	-3.74 to 25.14	0.1462

ΔDDS = mean difference between cases and matched controls in the number of days drug supplied; ΔTotal cost = mean difference between cases and controls in cost of medications; OCD = other cardiovascular drugs (see box 1); ACE-I = angiotensin converting enzyme inhibitors; CI = confidence interval.

Table 5 Predictors of medication use in the year prior to diagnosis in patients with OSAS

Risk factor	All drugs OR (95% CI)	Cardiovascular drugs OR (95% CI)	Antihypertensive drugs OR (95% CI)
Sex (female/male)	2.93 (1.49 to 5.76)	–	–
Age (per + 1 year)	1.05 (1.03 to 1.07)	1.11 (1.08 to 1.13)	1.10 (1.08 to 1.13)
BMI (per + 1 unit)	–	1.05 (1.02 to 1.08)	1.05 (1.02 to 1.08)
AHI (per + 1 unit)	–	–	1.01 (1.01 to 1.02)
Time <90% (per +1%)	–	1.02 (1.01 to 1.03)	–
ESS (per +1 point)	1.06 (1.02 to 1.10)	–	–

BMI=body mass index; AHI=apnoea/hypopnoea index; time <90%=percentage of time below an SaO_2 of 90%; ESS=Epworth sleepiness scale score; – = variable eliminated from model.

Illustrative examples to aid interpretation: compared with male OSAS patients, female patients are 2.93 more likely to use any medication, but there is no difference for cardiovascular drugs or antihypertensives. The odds of using any drug increases by 6% for one unit increase in ESS.

Figure 2 Effect of hypoxaemia (time <90%) on the estimated total cost of drugs for a 45 year old man with OSAS, AHI=45, BMI=35, ESS=13. The greater the sleep hypoxaemia, the more was spent on prescribed medications.

and AHI were predictors of antihypertensive drug use in patients with OSAS.

This analysis was performed for each antihypertensive drug. Table 6 shows that the use of diuretics and of ACE inhibitors was predicted by BMI and age. AHI was a predictor of diuretic and ACE inhibitor use and time<90% was a predictor of the use of loop diuretics. ESS did not predict the use of any cardiovascular drug.

Predicting cost of drugs in OSAS

Days of all drug supplied was significantly increased by age ($p<0.0001$), female sex ($p<0.0001$), BMI ($p=0.0042$), and

time<90% ($p=0.0005$), but not AHI or ESS. The cost of all drugs supplied was also significantly increased by the same variables: age ($p<0.0001$), female sex ($p<0.0034$), BMI ($p<0.0089$), and time<90% ($p=0.0012$, fig 2).

Interestingly, for cardiovascular drugs the only variable which significantly predicted increased DDS ($p<0.0001$) and cost ($p=0.0041$) was age.

DISCUSSION

Our study has shown that patients with OSAS are heavy users of prescribed medications, especially those for cardiovascular disease, before their OSAS diagnosis and treatment. This was true both for men and women. Our findings are consistent with previous studies that have shown that hypertension is more often diagnosed in these patients. The relative risk for being prescribed an antihypertensive agent compared with controls (2.71) in our patients is of the same order of magnitude as the odds ratio for hypertension reported in recent large studies that employed very different experimental designs.^{9, 10} For example, Peppard *et al* found that the odds ratio of having hypertension in subjects with an AHI of >15 was 2.89 relative to those with an AHI of zero.¹⁰ However, our data on the use of antihypertensive agents must be interpreted cautiously since clinicians might use these medications not just for controlling high blood pressure, but for other indications and benefits from reducing blood pressure such as the treatment of angina pectoris, congestive heart failure and the secondary prevention of myocardial infarction in high risk patients. There is no way to determine from the database the specific indication for which a drug is prescribed.

Table 6 Predictors of cardiovascular medication use in OSAS

Risk factor	Anti-adrenergic drugs	Diuretics	Loop diuretics	Beta blockers	Calcium channel blockers	ACE-I	OCD	Cholesterol and triglyceride reducers
Sex (female/male)	–	3.17 (1.74 to 5.75)	–	–	–	–	0.40 (0.16 to 1.00)	–
Age (per + 1 year)	1.09 (1.03 to 1.15)	1.07 (1.04 to 1.09)	1.09 (1.05 to 1.13)	1.06 (1.03 to 1.09)	1.07 (1.04 to 1.09)	1.07 (1.05 to 1.10)	1.09 (1.06 to 1.13)	1.07 (1.04 to 1.11)
BMI (per + 1 unit)	–	–	1.07 (1.02 to 1.12)	–	1.04 (1.01 to 1.07)	1.05 (1.02 to 1.08)	1.06 (1.01 to 1.11)	–
AHI (per + 1 unit)	1.02 (1.00 to 1.04)	1.02 (1.01 to 1.03)	–	–	–	1.01 (1.00 to 1.02)	–	–
Time <90% (per +1%)	–	–	1.02 (1.01 to 1.04)	–	–	–	–	–
ESS (per +1 point)	–	–	–	–	–	–	–	–

Values are odds ratio (95% confidence interval) with unit increase in variable.

ACE-I=ACE inhibitor; OCD=other cardiac drugs (see box 1); BMI=body mass index; AHI=apnoea/hypopnoea index; time<90%=percentage time below an SaO_2 of 90%; ESS=Epworth sleepiness scale score; – = variable eliminated from model.

Illustrative examples to aid interpretation: In OSAS patients, use of diuretics is more likely (317%) and that of OCD less likely (60%) in females than in males. One unit increase in AHI is associated with a 2% increase in the likelihood of using anti-adrenergic drugs or diuretics. In addition to age and BMI, AHI increases the probability of using ACE-I in OSAS patients. An increase in ESS is not associated with an increase in the use of cardiovascular medications. On the other hand, time <90% is associated with increased odds of using diuretics; and AHI with increased odds of using anti-adrenergic drugs, diuretics, and ACE-I.

Research has shown that sleep apnoea is an independent risk factor for the development of arterial hypertension. This research encompasses work in experimental animals,⁸ clinical studies,²³ epidemiological studies,^{9,10} and health care utilisation studies.²⁴ The latter study showed that health care cost, as measured by utilisation of health care resources (physician fees), was higher for hypertension in undiagnosed OSAS patients than in controls.

Our study extends the earlier studies showing that the use of medications in these patients is increased compared with matched controls. Patients with apnoea who are not yet receiving treatment are therefore very heavy users of health care resources as measured by physician fees, hospital admissions, and medication use.

Cases and controls were matched as closely as possible for sex, age, and postal code using data from the population registry. The postal codes were matched because it has been shown that use of health care resources varies with socioeconomic factors including area of residence. The population database does not store data such as weight or height so it was not possible to match these patients by BMI. Patients and controls had been matched to the same family physician and therefore this helped to control for the fact that different physicians may use different criteria and medications in their practice.

Women with OSAS were more likely to be using medications than men, but not for cardiovascular drugs or antihypertensives. It has previously been reported that women are heavier users of drugs than men.¹⁶

Our study suggests that there are differences between men and women with OSAS, with apnoea severity (AHI) being lower and both age and BMI higher in women than in men. In the year before OSAS diagnosis women had been on more drugs and had been dispensed many more prescriptions at a much greater cost than men. The reasons for these sex differences are not known.

It was not surprising to find that age was a predictor for use and cost of all drugs and cardiovascular drugs. Drug use has been shown to increase with age.¹⁶ BMI did not predict the use of all medications, but did predict the use of cardiovascular drugs. The cost of all drugs was increased by sleep hypoxaemia. The cases with more severe apnoea (as measured by AHI) were more likely to be on antihypertensive agents—for example, patients with an AHI of 60 had a 65% increase in odds ratio of being on an antihypertensive agent compared with those with an AHI of 10. In contrast to the study by Nieto *et al*⁹ which found that sleep hypoxaemia increases the risk of hypertension, we found that exposure to hypoxaemia did not predict the use of antihypertensive drugs but did predict the use of loop diuretics. The latter medications are used most often to treat oedema. It has been suggested that hypoxaemia plays a role in the development of cor pulmonale and oedema in OSAS.²⁵

We found that subjective sleepiness in OSAS patients predicted the use of all medications but not the subgroup of drugs used to treat cardiovascular disease. This suggests that either patients are on non-cardiovascular medications acting on the nervous system that are making them sleepy, and/or that more sleepy patients are being treated for another condition such as depression. It has been suggested that features of depression may be present in OSAS and that patients with OSAS are more likely to have been diagnosed with depression.^{26–28}

This research has established the usefulness of the DPIN database in evaluating drug use of specific patient groups and for specific drugs. Future studies we will examine medication use in other OSAS co-morbidities such as depression and evaluate the impact on medication use of treatment in patients with OSAS.

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