Evaluation of factors affecting adherence to asthma controller therapy in chest clinics in a sub-Saharan African setting: a cross-sectional study

Bertrand Hugo Mbatchou Ngahane[1,3], Eric Walter Pefura-Yone[2,4], Maïmouna Mama[3], Bruno Tengang[5], Motto Malea Nganda[3], Adeline Wandji[6], Ubald Olinga[2], Emmanuel Nyankiyé[7], Emmanuel Afane Ze[4], Christopher Kuaban[8]

1. Department of Internal Medicine, Douala General Hospital, Douala, Cameroon
2. Yaounde Jamot Hospital, Pneumology service, Yaounde, Cameroon
3. Faculty of Medicine and Pharmaceutical Sciences, University of Douala, Cameroon
4. Faculty of Medicine and Biomedical Sciences, Internal medicine and specialities, University of Yaounde I, Yaounde, Cameroon
5. Centre des Maladies Respiratoires, Douala, Cameroon
6. Douala Laquintinie Hospital, Cameroon
7. Cabinet de Pneumologie d'Akwa, Cameroon
8. Faculty of Health Sciences, University of Bamenda, Cameroon

Abstract:

Background: Adherence to controller therapy in asthma is a major concern during the management of the disease.

Objective: To determine the adherence rate and identify the predictors of low adherence to asthma controller therapy.

Methods: A cross-sectional study including asthma patients was conducted from November 1, 2012 to May 31, 2013 in 4 chest clinics in Cameroon. The adherence to asthma treatment was rated using Morisky Medication Adherence Scale. A multivariate logistic regression analysis was performed for the identification of factors associated with adherence to asthma treatment.

Results: Among the 201 asthma patients included, 133 (66.2%) were female. The mean age of participants was 41.2 years. Sixty-one (30.3%) of the patients did not visit the chest physician during the last year prior to the study. Asthma was well controlled in 118 patients (58.7%). The prevalence of low adherence rate to asthma controller therapy was 44.8% and the absence of any chest specialist visit within the last 12 months was the only factor associated with the low adherence rate to asthma treatment (OR 5.57 ; 95% CI 2.84–10.93).

Conclusion: The adherence rate to asthma controller therapy in Cameroon is low and it could be improved if scheduled visits are respected by patients.

Keywords: Allergy, medication adherence, Africa

DOI: http://dx.doi.org/10.4314/ahs.v16i1.26

Cite as: *Ngahane BHM, Pefura-Yone EW, Mama M, Tengang B, Nganda MM, Wandji A, Olinga U, Nyankiyé E, Afane Ze E, Kuaban C. Evaluation of factors affecting adherence to asthma controller therapy in chest clinics in a sub-SaharanAfrican setting: a cross-sectional study. Afri Health Sci. 2016;16(1): 194-200. http://dx.doi.org/10.4314/ahs.v16i1.26*

Introduction

Asthma is a heterogeneous disease, characterized by variable symptoms of wheeze, shortness of breath, chest tightness, and/or cough and by variable expiratory flow limitation[1]. It is one of the commonest chronic diseases in the world that affects about 300 million people[2]. In Cameroon, the estimated prevalence is 5.7% in adolescents aged 13 to 14 years[3]. The main goal of asthma treatment is to achieve and maintain good control of symptoms. This objective needs the acceptance of the diagnosis by the patient and the willingness to follow the recommendations provided by the physician. Adherence which is defined as the patient's behaviors regarding recommendations from a health care provider[4] is a crucial factor contributing to the control of asthma. A recent systematic review showed that good adherence to asthma medication is associated with low risk of severe exacerbation[5]. On the contrary, it has been demonstrated that low rate of adherence to asthma controller therapy is a risk factor for admission to the hospital, near-fatal asthma exacerbations, and death

Corresponding author:
Bertrand Hugo Mbatchou Ngahane,
PO Box 4856 Douala, Cameroon
Telephone: +(237) 697 068 899
Email: mbatchou.ngahane@yahoo.com

from asthma[6,7]. Furthermore, adherence is also associated with direct and indirect costs of care[8] and quality of life of asthma patients[9]. The introduction of inhaled corticosteroids in recent decades has improved the management of asthma. Corticosteroids are currently considered the cornerstone of maintenance therapy for asthma at all levels of severity in adults and children[4].

Adherence to inhaled corticosteroids is a prerequisite for the long term management of asthma. Less than 50% of children are adherent to this treatment while in the adult population, the adherence is also low with a highly variable range from 30 to 70% depending on the area where the studies have been conducted[5]. In Nigeria, Desalu et al. found that 69.3% of their study population had uncontrolled asthma and there was a strong association between uncontrolled asthma and lack of adherence to inhaled corticosteroids[10]. In western countries, this poor adherence to asthma controller therapy has been attributed to safety concerns towards the use of inhaled corticosteroids by patients[11].

In addition, other factors such as gender, age, ethnicity, socioeconomic status, psychological problems, fear, and misperceptions of asthma are associated with non adherence to asthma therapy. Besides regular health care visits, peak flow variability, and self-perceived severity of disease are correlated with a good adherence to asthma therapy[12]. The identification of factors related to the adherence to asthma controller therapy is invaluable for the effective management of asthma. Such knowledge could help to set up a strategy to improve adherence to treatment and could finally lead to the achievement of an optimal control of asthma. Therefore, the aim of the present study was to assess the adherence rates and to identify factors associated to low adherence to asthma controller medication in a sub-Saharan African setting.

Methods

Study design and setting

We conducted a cross-sectional study from 1st November 2012 to 31st May 2013 in the 4 chest specialist consultation clinics in the 2 biggest cities in Cameroon. The chest clinics of two tertiary care hospitals (Jamot Hospital in Yaounde and Douala General Hospital in Douala) and two private chest consultation centers (Centre des Maladies Respiratoires and Cabinet de Pneumologie d'Akwa) in Douala.

Participants

The study population consisted of asthma patients aged ≥ 12 years under an asthma controller therapy and who had consulted a chest physician within 2 years prior to the study. Subjects were invited through a telephone call to participate in the study. These patients had a written evidence of diagnosis of asthma by a chest physician. Patients with cardiac failure, chronic obstructive pulmonary disease, bronchiectasis, previous tuberculosis, lung tumors and other clinically significant respiratory diseases were excluded. The study protocol was reviewed and approved by the Cameroon National Ethics Committee.

Study procedure

Eligible participants were identified using consultation records obtained from the clinics. They were then invited through a telephone call to participate in the study. Upon their arrival at the study site, participants were given the information about the study and an oral consent was obtained before the enrolment. Study variables were collected using a questionnaire during a face to face interview.

Study variables

For each patient included in the study, the sociodemographic data was recorded (age, gender, level of education,medical insurance status). Medical history (hospitalization for an exacerbation, chest physician consultation, allergic rhinitis, gastro-oesophageal reflux), smoking status, alcohol consumption, body mass index (BMI), controller therapy (inhaled corticosteroids vs inhaled corticosteroid/long-acting beta-agonists) were also recorded. The level of asthma control was assessed during the past 4 weeks by the Asthma Control Test (ACT)[13]. An ACT score ≥ 20 indicates well controlled asthma, while 16 to 19 indicates partly controlled asthma and ≤ 15 characterizes poorly controlled asthma.

Adherence to asthma medication was assessed using the eight-item Morisky Medication Adherence Scale (MMAS-8)[14,15]. This patient-report measurement of treatment adherence has a maximum score of 8 points and is classified in 3 levels: low adherence (score < 6 points), medium adherence (score between 6 and 7 points) and high adherence (score = 8 points).

Data analysis

Data was analyzed using SPSS version 20. Descriptive statistics were used to report the baseline characteristics of the participants. Bivariate associations between treatment adherence and patient characteristics were tested using chi-square tests. During this analysis, asthma was

considered controlled for an ACT score ≥ 20 and uncontrolled for a score < 20. As dependant variable, low adherence category was compared with medium/high adherence category. Variables with a p-value less than 0.20 in the bivariate analysis were included in a multivariate logistic regression analysis for the examination of factors independently associated with the medication adherence. The odds ratio (OR) and its 95% confidence interval (CI) were determined for each variable. A p-value less than 0.05 was considered to be statistical significant.

Results

Among the 1063 patients registered in the 4 clinics, 466 were contacted and 243 came for the survey. Forty two of them were excluded because they were not on any controller medication. A total of 201 asthma patients were finally included in the study. Among these, 133 (66.2%) were female. The mean age of participants was 41.16 ± 18.9 years (range 12 – 87). The percentage of those covered by a medical insurance was 28.4% (57 participants) and 61(30.3%) of the participants had not attended a chest physician clinic for the last 12 months prior to the study. The mean BMI was 27 ± 6 kg/m2 (range 13.51 – 45.45). Asthma was well controlled in 118 patients (58.7%), partly controlled in 45 (22.4%) and poorly controlled 38 (18.9%). The mean MMAS-8 score was 5.52 ± 2.02 while 90 patients had a low rate of adherence to asthma controller medication, giving a prevalence of 44.8% (95% CI; 37.8 – 51.7). The adherence was medium for 73 (36.3%) and high for 38 (18.9%) patients. The other characteristics of the general population are shown in table 1.

Table 1: Baseline characteristics of participants (N=201)

Variables	Total	Low adherence	Medium adherence	High adherence
Age				
< 50 years	138 (68.7%)	69 (50%)	50 (36.2%)	19 (13.8%)
≥ 50 years	63 (31.3%)	21 (33.3%)	23 (36.5%)	19 (30.2%)
Gender				
Male	68 (33.8%)	35 (51.5%)	27 (39.7)	6 (8.8)
Female	133 (66.2%)	55 (41.4%)	46 (34.6)	32 (24.1%)
Level of education				
≤ Primary school	36 (17.9%)	11 (30.6%)	13(36.1%)	12 (33.3%)
≥ Secondary school	165 (82.1)	79 (47.9%)	60 (36.4%)	26 (15.7%)
Medical insurance				
Yes	57 (28.4%)	26 (45.6%)	26 (45.6%)	5 (8.8%)
No	144 (71.6%)	64 (44.5%)	47 (32.6%)	33 (22.9%)
Last hospitalization				
< 12 months	31 (15.5%)	15 (48.4%)	7 (22.6%)	9 (29%)
≥ 12 months	170 (84.5%)	75 (44.7%)	66 (38.8%)	28 (16.5%)
Chest physician visit				
≤ 12 months	140 (69.7%)	46 (32.9%)	57 (40.7%)	37 (26.4%)
> 12 months	61 (30.3%)	44 (72.1)	16 (26.2%)	1 (1.6%)
Asthma duration				
≤ 8 years	101 (50.2%)	47 (46.5%)	37 (36.6%)	17 (16.8%)
> 8 years	100 (49.8%)	43 (43%)	36 (36%)	21 (21%)
Alcohol consumption				
Yes	39 (19.4%)	16 (41%)	18 (46.2%)	5 (12.8%)
No	162 (80.6%)	74 (45.7%)	55 (34%)	33 (20.4%)
Obesity (BMI ≥ 30 kg/m^2)				
No	137 (68.1%)	67 (48.9%)	46 (33.6%)	24 (17.5%)
Yes	64(31.9%)	23 (35.9%)	27 (42.2%)	14 (21.9%)
Allergic rhinitis				
Yes	126 (62.7%)	60 (47.6%)	47 (37.3%)	19 (15.1%)
No	75 (37.3%)	30 (40%)	26 (34.7%)	19 (25.3%)
Gastro-oesophageal reflux				
Yes	28 (14.4%)	10 (35.7)	10 (35.7%)	8 (28.6%)
No	173 (85.6%)	80 (46.2%)	63 (36.4%)	30 (17.4%)
Asthma controller therapy				
ICS[a]	50 (24.9%)	22 (44%)	19 (38%)	9 (18%)
ICS + LABA[b]	151 (75.1%)	67 (45%)	54 (35.8%)	29 (19.2%)
Asthma control				
Well controlled	118 (58.7%)	50 (42.4%)	46 (39%)	22 (18.6%)
Partly uncontrolled	45 (22.4%)	21 (46.7%)	17 (37.8%)	7 (15.6%)
Poorly controlled asthma	38 (18.9%)	19 (44.8%)	10 (26.3%)	9 (23.7%)

[a]ICS: Inhaled corticosteroid [b]LABA: long-acting beta-agonists

The bivariate analysis (Table 2) shows that not visiting the chest specialist was significantly associated with low adherence to asthma medication.

Though not statistically significant, participants aged less than 40 years and those with at least a secondary education were more prone to have a low adherence rate to asthma treatment.

Table 2. Bivariate analysis of factors associated with adherence to asthma controller therapy (N=201)

Variables	Medication adherence		P value
	Low adherence	Medium/High	
Age			
< 40 years	49 (51%)	47 (49%)	0.08
≥ 40 years	41 (39%)	64 (61%)	
Gender			
Male	35 (51.5%)	33 (48.5%)	0.17
Female	55 (41.4%)	78 (58.6%)	
Levelof education			
≥ Secondary school	79 (47.9%)	86 (52.1%)	0.05
≤ Primary school	11 (30.6%)	25 (69.4%)	
Medical insurance			
Yes	26 (45.6%)	31 (54.4%)	0.88
No	64 (44.4%)	80 (55.6%)	
Ever Hospitalized for asthma	39 (48.1)	42 (51.9)	0.43
Yes	51 (42.5)	69 (57.5)	
No			
Lasthospitalization			
≥ 12 months	75 (44.4%)	94 (55.6%)	0.68
< 12 months	15 (48.4%)	16 (51.6%)	
Chest physician visit			
> 12 months	44 (72.1%)	17 (27.9)	< 0.001
≤ 12 months	46 (32.9)	94 (67.1)	
Duration of asthma			
≤ 8 years	47 (46.5)	54 (53.5)	0.61
> 8 years	43 (43)	57 (57)	
Alcohol consumption			
Yes	16 (41)	23 (59)	0.60
No	74 (45.7)	88 (54.3)	
Controlled asthma			
Yes (ACT ≥ 20)	50 (42.4%)	68 (57.6%)	0.41
No (ACT < 20)	40 (48.2%)	43 (51.8%)	
Asthma controller therapy			
ICS	22 (44)	28 (56)	0.93
ICS + LABA	67 (44.7)	83 (55.3)	

In the multivariate model (Table 3), the only variable independently associated with the low rate of medication adherence was the absence of chest physician consultation during the last 12 months prior to the study (OR 5.57; 95% CI 2.84 – 10.93).

Table 3. Multivariate analysis of factors associated with adherence to asthma controller therapy (N=201)

Variables	Medication adherence		aOR[a] (95% CI)	P value
	Low adherence	Medium/High		
Age				
< 40 years	49 (51%)	47 (49%)	1.83 (1.00 – 3.37)	0.05
≥ 40 years	41 (39%)	64 (61%)		
Gender				
Male	35 (51.5%)	33 (48.5%)	1.21 (0.64 – 2.31)	0.54
Female	55 (41.4%)	78 (58.6%)		
Level of education				
≥ Secondary school	79(47.9%)	86 (52.1%)	1.7 (0.70 – 4.07)	0.23
≤ Primary school	11 (30.6%)	25 (69.4%)		
Chest physician visit				
> 12 months	44 (72.1%)	17 (27.9)	5.57 (2.84 – 10.93)	< 0.001
≤ 12 months	46 (32.9)	94 (67.1)		

[a]aOR: Adjusted odds ratio

Discussion

This study was carried out to assess controller therapy adherence among asthma patients. Adherence to treatment is considered the major factor influencing the control of asthma[16,17]. In the present study, we found a low adherence to treatment among our patients and only 18.9% of the sample population had high adherence rate. The only factor independently associated with low adherence to asthma controller therapy was not having visited the chest specialist during the previous 12 months. Age older than 40 years was at the border of statistical significance.

This result shows that a substantial proportion of asthma patients do not adhere to the asthma controller therapy and this finding is consistent with some previous studies in which the Morisky scale was used to assess adherence to asthma medication. In fact, a study conducted in four Asian countries among 1054 asthma patients also found an adherence rate of 18.9%[18]. Another study involving 1410 patients with persistent asthma showed that 20.7% of them were highly adherent to inhaled corticosteroids therapy[19]. These rates are considerably lower than the 60% reported by Demoly et al in a community-based survey that involved five European countries[20]. In a tertiary care setting in Nigeria, Desalu et al. found 80.4% of low adherence to inhaled corticosteroid reported by patients[10]. This proportion is higher than our finding probably because the methods used to define low adherence were not similar in the two studies.

The present study also showed that no visit of the asthma patients to a chest physician in the last 12 month prior to the study was the only independent predictor of treatment adherence. Similar results were found by Corsico et al in European Community Respiratory Health Survey study of 971 subjects with asthma[21]. In fact, it has been demonstrated that regular follow up consultations with clinicians reinforce the partnership between patients and healthcare workers with a subsequent positive effect on the medication adherence[22-24].

We found that asthma patients older than 40 years had a better adherence to asthma treatment. This finding corroborates the results of previous studies showing that the adherence to asthma controller therapy increases with age[25,26]. On the contrary, Apter et al did not observe any relationship between age and adherence to asthma controller mediation in a similar study in the United States[27]. Interestingly, in another study involving elderly asthma patients aged 65 years and above, the treatment adherence was very low[28]. These conflicting results are probably due to the differences in the methods used to assess adherence in these studies. Future research using a better method of assessment of medication adherence such as electronic monitor devices[29,30] is needed to conclude on any relationship between age and adherence to asthma controller therapy.

Although the proportion of patients with low adherence was greater among patients with uncontrolled asthma (84.2%) than in patients with controlled asthma (42.4%), the difference was not statistically significant. The absence of correlation between this two variables could be explained by the fact that some patients may have misestimated their asthma control and adherence to medication.

We did not find any relationship between sex, level of education, possession of medical insurance, duration of asthma, hospitalization for asthma and adherence to asthma controller medication. Conflicting results have been reported concerning the effect of sex on adherence to asthma medication[21,25,31] as well as that of education level and medical insurance coverage[12,29,30].

This study which is among the first to assess adherence to asthma medication in sub-Saharan Africa has some limitations. Firstly, although the Morisky scale has been validated in the measurement of treatment adherence, it is a self-reported method and patients may have wrongly estimated their adherence to asthma treatment. Secondly, other characteristics such as inhalation technique, the socioeconomic status and knowledge of asthma were not investigated as factors associated with asthma medication adherence. The small size of the sample may have also underpowered the study.

Conclusion

The adherence rate to asthma controller therapy in chest clinics in Cameroon is very low. Less frequent visits to the chest physician is the main contributor to this low adherence. These findings constitute additional evidence that there is considerable need for improvement in treatment adherence among sub-Saharan African asthma patients. Education of patients on the importance of maintenance therapy during scheduled visit would surely contribute to the increase of adherence rate to asthma treatment.

Contribution of authors:

MNBH conceived the study, designed the protocol, analyzed the data and drafted the manuscript. PYEW participated to acquisition of data and revised the manuscript. MM collected the data and approved the manuscript. NMM revised the manuscript. OU, TB, NE, AZE participated to acquisition of data and approved the manuscript. KC designed the protocol, revised and approved the manuscript.

Declaration of interest:

None declared.

Acknowledgements:

Many thanks to all asthma patients who agreed to participate in this study. The authors also thank the Pan African Thoracic Society MECOR course staff for their contribution during the preparation of this manuscript.

References

1. GINA. Global Initiative For Asthma. Global Strategy for Asthma Management and Prevention 2014.
2. GINA. Global Initiative For Asthma. Global Burden of Asthma 2004. Available from: www.ginasthma.org. Accessed September 2014.
3. Ait-Khaled N, Odhiambo J, Pearce N, et al. Prevalence of symptoms of asthma, rhinitis and eczema in 13- to 14-year-old children in Africa: the International Study of Asthma and Allergies in Childhood Phase III. *Allergy.* 2007 Mar;62(3):247-58.
4. Horne R. Compliance, adherence, and concordance: implications for asthma treatment. *Chest.* 2006 Jul;130(1 Suppl):65S-72S.
5. Engelkes M, Janssens HM, de Jongste JC, Sturkenboom MC, Verhamme KM. Medication adherence and the risk of severe asthma exacerbations: a systematic review. *Eur Respir J.* 2014 Oct 16.
6. Dhuper S, Maggiore D, Chung V, Shim C. Profile of near-fatal asthma in an inner-city hospital. *Chest.* 2003 Nov;124(5):1880-4.
7. Stern L, Berman J, Lumry W, et al. Medication compliance and disease exacerbation in patients with asthma: a retrospective study of managed care data. *Ann Allergy Asthma Immunol.* 2006 Sep;97(3):402-8.
8. Bender BG, Rand C. Medication non-adherence and asthma treatment cost. *Curr Opin Allergy Clin Immunol.* 2004 Jun;4(3):191-5.
9. Cote I, Farris K, Feeny D. Is adherence to drug treatment correlated with health-related quality of life? *Qual Life Res.* 2003 Sep;12(6):621-33.
10. Desalu OO, Fawibe AE, Salami AK. Assessment of the level of asthma control among adult patients in two tertiary care centers in Nigeria. *J Asthma.* 2012 Sep;49(7):765-72.
11. Chan PW, DeBruyne JA. Parental concern towards the use of inhaled therapy in children with chronic asthma. *Pediatr Int.* 2000 Oct;42(5):547-51.
12. Howell G. Nonadherence to medical therapy in asthma: risk factors, barriers, and strategies for improving. *J Asthma.* 2008 Nov;45(9):723-9.

13. Nathan RA, Sorkness CA, Kosinski M, et al. Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol.* 2004 Jan;113(1):59-65.
14. Morisky DE, Ang A, Krousel-Wood M, Ward HJ. Predictive validity of a medication adherence measure in an outpatient setting. *J Clin Hypertens* (Greenwich). 2008 May;10(5):348-54.
15. Morisky DE, DiMatteo MR. Improving the measurement of self-reported medication nonadherence: response to authors. *J Clin Epidemiol.* 2011 Mar;64(3):255-7; discussion 8-63.
16. Boulet LP, Vervloet D, Magar Y, Foster JM. Adherence: the goal to control asthma. *Clin Chest Med.* 2012 Sep;33(3):405-17.
17. Stempel DA, Roberts CS, Stanford RH. Treatment patterns in the months prior to and after asthma-related emergency department visit. *Chest.* 2004Jul;126(1):75-80.
18. Chiu KC, Boonsawat W, Cho SH, et al. Patients' beliefs and behaviors related to treatment adherence in patients with asthma requiring maintenance treatment in Asia. *J Asthma.* 2014 Aug;51(6):652-9.
19. Ivanova JI, Birnbaum HG, Hsieh M, et al. Adherence to inhaled corticosteroid use and local adverse events in persistent asthma. *Am J Manag Care.* 2008 Dec;14(12):801-9.
20. Demoly P, Gueron B, Annunziata K, Adamek L, Walters RD. Update on asthma control in five European countries: results of a 2008 survey. *Eur Respir Rev.* 2010 Jun;19(116):150-7.
21. Corsico AG, Cazzoletti L, de Marco R, et al. Factors affecting adherence to asthma treatment in an international cohort of young and middle-aged adults. Respir Med. 2007 Jun;101(6):1363-7.
22. Caress AL, Beaver K, Luker K, Campbell M, Woodcock A. Involvement in treatment decisions: what do adults with asthma want and what do they get? Results of a cross sectional survey. *Thorax.* 2005 Mar;60(3):199-205.
23. Onyirimba F, Apter A, Reisine S, et al. Direct clinician-to-patient feedback discussion of inhaled steroid use: its effect on adherence. *Ann Allergy Asthma Immunol.* 2003 Apr;90(4):411-5.
24. Partridge MR. The asthma consultation: what is important? *Curr Med Res Opin.* 2005;21 Suppl 4:S11-7.
25. Bae YJ, Kim TB, Jee YK, et al. Severe asthma patients in Korea overestimate their adherence to inhaled corticosteroids. *J Asthma.* 2009 Aug;46(6):591-5.
26. Rolnick SJ, Pawloski PA, Hedblom BD, Asche SE, Bruzek RJ. Patient characteristics associated with medication adherence. *Clin Med Res.* 2013 Jun;11(2):54-65.
27. Apter AJ, Boston RC, George M, et al. Modifiable barriers to adherence to inhaled steroids among adults with asthma: it's not just black and white. *J Allergy Clin Immunol.* 2003 Jun;111(6):1219-26.
28. Bozek A, Jarzab J. Adherence to asthma therapy in elderly patients. *J Asthma.* 2010 Mar;47(2):162-5.
29. Fish L, Lung CL. Adherence to asthma therapy. *Ann Allergy Asthma Immunol.* 2001 Jun;86(6 Suppl 1):24-30.
30. Gillisen A. Patient's adherence in asthma. *J Physiol Pharmacol.* 2007 Nov;58 Suppl 5(Pt 1):205-22.
31. Janson C, de Marco R, Accordini S, et al. Changes in the use of anti-asthmatic medication in an international cohort. *Eur Respir J.* 2005 Dec;26(6):1047-55.