Clinical factors associated with the overuse of asthma rescue medication

Brief running title

Factors associated with rescue therapy overuse

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Abstract

Objective: Our aim was to evaluate the relationship between asthma clinical factors and use of relief medication.

Methods: This was an observational cross-sectional study conducted in Spain. The study recruited patients ≥ 12 years of age diagnosed with persistent asthma according to the GINA criteria and receiving maintenance treatment for at least 12 months. Use of relief medication was dichotomized: low use of rescue medication (LURM) (≤ twice/week) or high use of rescue medication (HURM) (≥ three times/week). A variety of clinical variables and patient reported outcomes (PROs) such as the Asthma Control Questionnaire-5 (ACQ-5) and Test of Adherence to Inhalers (TAI) were recorded.

Results: A total of 406 patients were recruited, mean (SD) age 44.3(17.9) years and 64% women. In 76.1% rescue medication was used ≤ twice/week. Bivariate analysis showed HURM was related to smoking habit, unscheduled emergency room visits, hospital admissions, increased inhaled corticosteroid doses, therapeutic upgrading and night awakenings in the last four weeks ($p<0.001$). The multivariate analysis showed a higher risk of using relief medication in smokers and former smokers, when the number of night awakenings increased, in cases of self-perception of partially controlled or uncontrolled asthma, or when asthma is uncontrolled according to ACQ-5.

Conclusions: Our study identifies the potential of using abuse of rescue medication in the last week as an alarm signal for disease parameters such as exacerbations, poor asthma control and disease severity.

Keywords: Relief medication, rescue medication, asthma control.

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Resumen

Objetivo: nuestro objetivo fue evaluar la relación entre parámetros clínicos del asma y el uso de medicación de rescate.

Métodos: estudio observacional de corte transversal realizado en España. El estudio reclutó pacientes ≥ 12 años diagnosticados con asma persistente según los criterios de GINA y que recibieron tratamiento de mantenimiento durante al menos 12 meses. El uso de la medicación de rescate fue dicotomizado: bajo uso de medicación de rescate (LURM) (≤ dos veces / semana) o alto uso de medicación de rescate (HURM) (≥ tres veces / semana). Se registraron una variedad de variables clínicas y resultados notificados por los pacientes (PRO), como el Cuestionario de Control del Asma-5 (ACQ-5) y la Prueba de Adherencia a Inhaladores (TAI).

Resultados: Se reclutaron 406 pacientes, de 44,3 (17,9) años edad media (DE) y un 64% de mujeres. En el 76,1% se utilizó medicación de rescate ≤ dos veces por semana. El análisis bivariante mostró que la HURM estaba relacionada con el hábito de fumar, las visitas no programadas a urgencias, ingresos hospitalarios, aumento de las dosis de corticosteroides inhalados, aumento en la terapia y los despertares nocturnos en las últimas cuatro semanas (p <0,001). El análisis multivariado mostró un mayor riesgo de usar medicación de rescate en fumadores y exfumadores, cuando aumentó el número de despertares nocturnos, en casos de autopercepción de asma parcialmente controlada o no controlada, o cuando el asma no está controlada en base al ACQ-5.

Conclusiones: nuestro estudio identifica la posibilidad de utilizar el aumento de la medicación de rescate en la última semana como una señal de alarma para algunos parámetros de la enfermedad, como exacerbaciones, mal control del asma y gravedad de la enfermedad.

Palabras clave: Asma, medicación de rescate, control del asma.

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Introduction

Despite the availability of effective treatments and consensus guidelines for the management of asthma [1, 2, 3] disease control is still suboptimal in approximately half the patients treated in Europe [4-7], and this is consistent with data from Spain [8]. In addition, there is evidence that poor asthma control is associated with an increased risk of exacerbations, a decrease or deterioration in quality of life, a reduction in productivity, and an increase in the use of health resources [6, 7, 9, 10]. Furthermore, the lack of control has been associated with an increased risk of hospitalization [11].

In clinical practice, the REcognise Asthma and LInk to Symptoms and Experience (REALISE) survey evaluated the social aspects, symptoms, levels of asthma control according to guidelines, and how the symptoms and indicators of exacerbations were related to this control and therapeutic steps in 8,000 patients from 11 European countries [12]. Their results showed that 45% of patients had poor disease control and more than 40% used their relief medication three or more times during the previous week. Those who used inhaled corticosteroid (ICS) and a long-acting beta-agonist (LABA) combination in an inhaler had the most frequent use (≥10 times in the previous week). Also, 50% of patients responded that they did not take their maintenance therapy as prescribed, and more than half had their inhaler technique reviewed by their doctor in the past year.

Asthma patients have great confidence in relief medication and some patients do not recognize this use as a sign of asthma deterioration and need for treatment adjustment. Patients' perceptions of their asthma control differ from the actual degree of control. Many patients with asthma do not consider themselves sick and are not worried about their condition. Since they believe their disease iscontrolled, they do not associate their symptoms with poor control. In fact, they overestimate their control and underestimate the severity of their disease, indicating that patients tolerate their symptoms and the limitations they cause [6, 13].

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Rescue therapies, such as short-acting beta agonists (SABAs), should be reserved for occasional use to relieve symptoms [12, 13]. However, SABAs are the primary mode of treatment for many patients [15, 16]. The aim of the present study was to evaluate the relationship between the use of relief medication (adequate or excessive use) and asthma clinical factors. We also assessed if abusing SABAs was a marker of poor asthma control in patients with persistent asthma who used high doses of relief medication while on inhaled maintenance therapy for at least one year.

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Patients and Methods

This was a real-world observational cross-sectional study conducted by Spanish pulmonologists, allergists, and general practitioners according to the International Guidelines for Ethical Review of Epidemiological Studies, the Declaration of Helsinki and all its amendments, and national regulations. The study was approved by the Ethics Committee of Hospital de la Santa Creu i Sant Pau (Spain) and all patients provided their written informed consent to participate.

Patient population

Patients were recruited using a consecutive non-probability sampling technique during a 3-month period. The study recruited patients ≥ 12 years of age diagnosed with persistent asthma, according to the Global Initiative for Asthma (GINA) criteria, at least 12 months before the inclusion date. Patients had to have used maintenance therapy for at least 12 months before inclusion; although, they may have received various other treatments steps throughout the year. Patients were excluded if they had already participated in a clinical trial in the last three months; had another severe illness that altered perception, such as fibromyalgia, severe anxiety, depression, or schizophrenia; were not able to understand the information provided in the Patient Information Sheet; or were not able to provide informed consent.

Evaluation of patients' characteristics

The type of relief medication used and the number of administrations within the past 30 days was recorded to characterize relief medication. For asthma control status, we used the Asthma Control Questionnaire-5 (ACQ-5) [8] scores: controlled (≤0.75), partially controlled (0.76-1.49), and uncontrolled (≥1.5). Additionally, asthma control was assessed according to the Spanish Guideline on the Management of Asthma (GEMA) guidelines [3], and self-perception of the degree of asthma control was measured using a Likert-type scale, where asthma was graded as controlled, partially controlled, or not controlled. Each patient reported exacerbations, which were confirmed in the clinical history. An exacerbation was defined as an acute

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worsening of asthma symptoms leading to the need to increase the dose of ICS or to increase treatment by one step, use of systemic corticosteroids, visits to the ER, other unscheduled health care visits, or need for hospitalization. Physicians also collected information about the patients' sociodemographic factors, smoking habits (smoker, former smoker, or non-smoker), asthma clinical history (date of diagnosis, severity of the disease, number of emergency visits in the last year, number of admissions, unscheduled visits, number of days with night awakenings within the previous 4 weeks, average consumption of relief medication per week, type of drugs on demand for the relief of symptoms), concomitant diseases, chronic concomitant treatment, and maintenance treatment for asthma. Finally, adherence to maintenance treatment was assessed through the Test of Adherence to Inhalers (TAI) questionnaire [18]. It has ten self-administered questions for the patient and two for the healthcare professional that define the degree of adherence and suggest the pattern of non-compliance to inhalation therapy (erratic, deliberate, or unwitting).

Statistical considerations

For sample size calculation, it was estimated that 60.2% [10] of patients using treatments similar to the study treatment are controlled and, therefore, a ratio of 1.5 to 1 of controlled to uncontrolled patients was expected. As there were no reported data on the relationship between control and excessive use of relief medication or on the proportion of patients with adequate vs. excessive use, the principle of maximum variance (50%) was assumed. Assuming an alpha risk of 0.05, a power of 80% in a two-sided test, and a maximum patient loss of 5%, it would be necessary to include 300 patients who were expected to be controlled and 200 who were expected to be uncontrolled to detect a ≥13% difference between groups.

For the statistical analysis, the use of relief medication was dichotomized into two groups: low use of rescue medication (LURM) (≤ twice per week) or high use of rescue medication (HURM) (≥ three times per week), according to the criteria of the GINA and GEMA 4.0 guidelines [3]. For the variables that were not adjusted to the normal (or parametric)

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distribution, Mann-Whitney hypothesis tests (for unpaired data) were used. In the analysis of the contingency tables, as well as for the comparison of distributions, Fisher's exact test was used. A logistic regression analysis was carried out to identify factors related to asthma control. The factors included were age, gender, smoking habit, asthma severity, number of uses of relief medication, number of hospital admissions, number of exacerbations, type of rescue medication, nasal polyposis, and self-perception of asthma control. Finally, an exploratory multivariate analysis of the use of relief medication $<$ vs. $\geq$ three times per week was built using the following factors: smoking habit, time from diagnosis, asthma severity, visits to ER, night awakenings, hospital admission, therapy increases, unscheduled visits, therapy step upgrading, exacerbations, self-perception of asthma control, ACQ-5 score, unwitting non-adherence, concomitant respiratory or skin disease, and maintenance therapy. Only factors that reach a p-value <0.20 in the bivariate analyses were included in each multivariate model. The data were analyzed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, Illinois, USA) v 18.0.

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Results

Patients' characteristics

A total of 407 patients participated in the study from November 2016 to February 2017; one of these patients was excluded due to a severe illness that altered patient perception. In the whole population, the main comorbidities were rhinitis (48.5%), hypertension (17%), gastroesophageal reflux (11%), nasal polyposis (9.4%), dyslipidemia (6.7%), atopic dermatitis (6.7%), diabetes (4.4 %), and COPD (1.5%) (Table 1). The asthma therapies are described in Table 2. The mean (SD) number of inhalations in the last seven days was 2.8 (6.2). Over the previous 30 days, the mean (SD) number of days using relief medication was 7.2 (20.3) days.

When evaluating asthma maintenance therapy in LURM and HURM patients, 15.5% and 16.5% of the patients used only ICS ($p=0.873$), 85.8% and 89.7% used a combination of ICS and LABA ($p=0.393$), 31.7% and 44.3% used a leukotriene receptor antagonist ($p<0.05$), 9.4% and 10.3% used anti-IgE (omalizumab) ($p=0.844$), and 1% and 10.3% used systemic corticosteroids ($p<0.001$). Most patients used rescue medication ≤ twice per week (76.1%) and almost a quarter of the study population showed abusive use. In Table 1, we present the main characteristics of the overall analyzed sample and when patients were divided by their frequency of use of asthma rescue medication. The frequency of smokers was higher in HURM vs. LURM patients; while, a sedentary lifestyle was more prevalent in patients with abusive use of rescue medication. The HURM group showed higher severity of asthma than the LURM group. Furthermore, the HURM group had more visits to ER in the last year, night awakenings in the last 4 weeks, hospital admissions in the last year, increases in ICS therapy in the previous year, unscheduled visits in the previous year, and upgraded therapeutic steps.

According to the TAI results, adherence to maintenance therapy was suboptimal, as 67% and 70.1% of LURM and HURM patients, respectively, were non-adherent ($p=0.620$). It is notable that the prevalence of the unwitting pattern of non-adherence was higher in HURM patients than

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LURM patients (21.6% vs. 12.9%, p=0.05) (Figure 1). No significant differences in the remaining patterns were noted, 64.4% and 68% of LURM and HURM patients, respectively, were erratic and 41.1% and 46.4% of LURM and HURM patients, respectively, were deliberate. The HURM patients had a lower level of asthma control (p<0.001) (Figure 2). When patients were asked about their perception of asthma control, 26.6% perceived asthma to be partially controlled and 10.6% uncontrolled. The concordance between ACQ scores and patient self-perception was moderate (Kappa index =0.476).

The logistic regression analysis model of factors related to asthma control showed that older patients, with moderate asthma severity, ≥3 uses of relief medication, and who received salbutamol or beclomethasone-formoterol in the last 30 days were less likely to achieve asthma control (Table 3). In the exploratory model of factors related to the use of rescue medication, there was a higher risk of using relief medication in smokers and former smokers, when the number of night awakenings increased, when there was self-perception of partially controlled or uncontrolled asthma, or when asthma was uncontrolled according to the ACQ-5 (Table 4).

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Discussion

This study supports an association between excessive use of relief medication and a poor degree of asthma control in patients on maintenance therapy. It also offers an overview of patients who abuse rescue medication, highlighting that factors such as smoking, night awakenings, or control assessed with the ACQ-5 are related to abusive use of rescue therapy. These findings can be incorporated into daily clinical practice. Although abuse of rescue medication is an issue that has been widely investigated, the study design and the definition of abuse differ between studies. Fitzgerald et al. [19] defined inappropriate use as two or more puffs of SABA per week in the absence of any ICS or use of more than nine canisters of SABA during the year and no more than 100 µg/day of ICS. Patel et al. [20] considered extreme use as >32 puffs of salbutamol in any 24-hour period. Belhassen et al. [21] described SABA overuse as ≥12 prescriptions/dispensations over 12 months; while, Lynd et al. [22] defined excessive use as >20 canisters in a calendar year, a criterion that was adopted in the recently published work of Tavakoli et al. [23]. We evaluated rescue medication used in the previous week. This, was based on GINA and U.S. guidelines, which indicate that the use of reliever medication more than twice per week is suggestive of poor control (24), a parameter that can easily be collected in the clinical practice. Regarding this criterion, nearly a quarter of the overall sample had inappropriate use of rescue medication in our study. The criterion most similar to ours was that used by Fitzgerald et al. (19) evaluated inappropriate SABA use in 343,520 patients, who contributed 2,127,592 patient-years of follow-up, but they found only 7.7% of patients inappropriately used rescue medication.

The outcomes associated with inappropriate use of SABAs have been extensively studied [25-27] and some reports provide factors that may be predictive of abusive use of SABAs. In 2013, Patel et al. [28] published a study that related the use of salbutamol with the risk of future severe exacerbations, inadequate asthma control, and extreme overuse of salbutamol. In this study, the univariate analyses showed that a Maori ethnicity, a higher number of severe exacerbations in the preceding 12 months, a higher number of hospital admissions at any time, higher self-

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reported reliever use, lower forced expiratory volume in 1 s (FEV_1) %, and standard therapy were associated with an increased risk of subsequent SABA overuse. Fitzgerald et al. reported that inappropriate SABA use was related to both hospital admissions and ER visits. The recently published database study by Tavakoli et al. [23] evaluated a cohort of 343,520 individuals, and identified variables such as sex, age, having a pulmonary function test, consulting a pulmonologist, consulting an allergist, visits to the physician, asthma-related hospitalization, appropriate use of ICS, use of systemic corticosteroids, comorbidities, and the use of health resources as factors associated with an increased likelihood of SABA overuse. In all cases, applicability of the results lies in identifying potential modifiable factors that can be taken into account when assessing the patient with asthma under treatment. The clinician can evaluate the presence or absence of these risk factors (e.g. age, lower FEV_1 %, etc.) to decide whether to implement support measures or stricter monitoring. In our case, the perspective was slightly different, as we pointed out a factor that may alert the clinician to a situation of disease deterioration. Our hypothesis was that patients with deteriorated clinical asthma factors would abuse rescue medication. As expected, there was a relationship between the abuse of relief medication and the patient's asthma control as well as the severity of the disease. The greater the severity, the greater the use of relief medication. GEMA and GINA guidelines also identified some clinical parameters as markers of poor control or disease worsening in the definition of the exacerbation as: "an acute worsening of asthma symptoms leading to the need to increase the dose of ICS or to increase treatment by one step, use of oral or systemic corticosteroids, visits to the ER or other unscheduled health care visits, or need for hospitalization" [3]. In our study, abusive use of rescue medications in the last week was related to the following clinical variables: the number of visits to ER in the last year, hospital admission in the last year, increase in ICS therapy in the previous year, unscheduled visits in the previous year, and therapeutic step upgrades, which were higher in the HURM patients. Other clinical variables, such as the number of night awakenings in the last 4 weeks, smoking habits, and a

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sedentary lifestyle were more prevalent in patients with abusive use of rescue medication. Finally, our study showed no relationship between the number of relief medication uses and eosinophilia, although they are both markers of asthma severity (one a clinical variable and the other a laboratory variable) and are not associated with each other. We considered that this lack of relationship was likely due to different degrees of disease severity in the study population. Our results are very similar to those reported by Tavakoli [23], except we did not compare factors such as sex or age that did not differ between groups and comorbidities. However, our study evaluated current clinical measures and information reported directly from the patient (e.g. control and adherence measurements).

Our results on adherence are contradictory. We expected that a misuse of maintenance medication would be related to increased use of rescue medication, but our results did not confirm this. In our population, patients were predominantly adherent. the TAI validation to Spanish study (29) in which 62.5% of patients were non-adherent, we obtained the same percentage but summing good and intermediate adherence, and of the 76.2% of patients with poor adherence used rescue medication two or fewer times per week. It is worth mentioning the significant relationship between [28] the unwilling pattern and the abuse of relief medication. Patients may not be aware of their lack of adherence and its impact on asthma symptoms, and this provides an opportunity to establish corrective measures in daily practice, such as patient education in the use and management of inhalers.

The main strength of this work was identifying the potential of abusing rescue medication in the last week, an extremely easy parameter to obtain, as an indicator of patient deterioration in terms of exacerbations, asthma control, and disease severity. There are also limitations that should be considered when interpreting the findings. The cross-sectional design of the study precludes establishing casual relationships and therefore further analysis of risk ratios cannot be done. This must be taken into account when interpreting our results, as we cannot affirm whether abusive use of rescue medication is the cause or the consequence of the lack of any of

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the related factors. Finally, the authors considered that the choice of the TAI could have affected the result obtained because patient reported outcomes are influenced by the patient's self-perception. Thus, it would be advisable to use electronic tools to demonstrate the relationship between abusive use of rescue medication and adherence in future studies. Finally, it is pertinent to state that sample size was not completely achieved, although this fact did not seem to affect finding some differences between the groups, in the case of adherence we cannot rule out an influence.

Conclusions

In conclusion, our study highlights the importance of rescue medication in the last week as a surrogate marker of poor asthma control, exacerbations, and disease severity. Unlike some variables that require going back to the clinical history of the previous year, the patient can easily provide information on their use of rescue medication in the last week; thus, this factor can be incorporated into daily clinical practice without difficulty. Nonetheless, the authors recognize that prospective follow-up studies are needed to discern its implication in the causal relationship between these factors and the use of rescue medication.

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Ethical statement

This study was conducted according to the International Guidelines for Ethical Review of Epidemiological Studies, the World Medical Association Declaration of Helsinki and all its amendments, and national regulations.

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Tables legends

Table 1. Patients' characteristics

	Total (n= 406)	LURM (≤ 2 times/week) (n= 309)	HURM (≥ 3 times/week) (n= 97)	p-value (between subgroups)
Age, mean (SD)	44.3 (17.9)	44.1(18.5)	44.9 (15.9)	0.689
Gender, n (%)				
Women	260 (64)	194 (62.8)	66 (68.0)	0.396
Smoking habit, n(%)				
Smoker	41 (10.1)	22 (7.1)	19 (19.6)	p<0.001
Former smoker	114 (28.1)	81 (26.2)	33 (34.0)	
No smoker	251 (61.8)	206 (66.7)	45 (46.4)	
Mean (SD) time from diagnosis	13.2 (11.2)	13.6 (11.1)	12.0 (11.6)	0.098
Asthma severity, n(%)				
Mild	95 (23.4)	85 (27.5)	10 (10.3)	<0.001
Moderate	218 (53.7)	168 (54.4)	50 (51.5)	
Severe	93 (22.9)	56 (18.1)	37 (38.1)	
Mean (SD) last eosinophil value count	0.5 (0.7)	0.5 (0.8)	0.5 (0.6)	p=0.442
Mean (SD) number of visits to ER in the last year	0.6 (1.2)	0.3 (0.8)	1.3 (1.9)	<0.001
Mean (SD) number of night awakenings in the	1.9 (5.6)	0.6 (1.4)	6.0 (10.1)	<0.001

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last four weeks				
Mean (SD) hospital admission in the last year	0.1 (0.4)	0.1 (0.3)	0.2 (0.6)	<0.001
Mean (SD) rise of ICS therapy in the last year	0.5 (1.0)	0.4 (0.8)	1.0 (1.4)	<0.001
Mean (SD) unscheduled visits in the last year	0.8 (1.8)	0.5 (0.9)	1.7 (3.2)	<0.001
Mean (SD) of a therapeutic step upgrade	0.5 (1.0)	0.4 (0.8)	0.9 (1.3)	<0.001
Mean (SD) asthma exacerbations in the last year	1.3 (2.3)	0.9 (2.0)	2.4 (2.9)	<0.001

LURM: low use of rescue medication; HURM: high use of rescue medication.

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Table 2. Asthma treatments

	N(%)
Monotherapy, n(%)	64 (15.8)
Budesonide	35 (8.6)
Fluticasone propionate	12 (3.0)
Mometasone furoate	10 (2.5)
Combination therapy	352 (86.7)
Budesonide/formoterol	125 (30.8)
Beclometasone/formoterol	84 (20.7)
Fluticasone propionate/salmeterol	72 (17.7)
Fluticasone propionate/formoterol	37 (9.1)
Fluticasone fuorate/vilanterol	36 (8.9)
Other therapies	
Long-acting muscarinic antagonist (LAMA)	42 (10.3)
Leukotriene receptor antagonists	141 (34.7)
Oral corticosteroids	13 (3.2)
Anti IgE-Omalizumab	39 (9.6)
Inmunotherapy	34 (8.4)
Rescue therapy in the last 7 days	
Salbutamol	136 (33.5)
Terbutaline	52 (12.8)
Ipratropium bromide	19 (4.7)
Budesonide/formoterol	20 (4.7)
Beclometasone/formoterol	15 (3.7)
Fluticasone propionate/formoterol	2 (0.5)

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Table 3. Multivariate analysis of factors related to asthma control

	B	E.T.	Sig.	Exp(B)	95% CI	
					Low	High
Age	-.021	.008	**.013**	**.980**	.964	.996
Asthma severity (reference: mild)			**.022**			
Moderate	-.910	.356	**.011**	**.403**	.200	.809
Severe	-.247	.449	.583	**.782**	.324	1.884
Number of uses of relief medication	-1.694	.490	**.001**	**.184**	.070	.480
Salbutamol	-1.239	.317	**.000**	**.290**	.156	.539
Beclometasone-Formoterol	-1.970	.862	**.022**	**.139**	.026	.755
Terbutaline	-1.259	.478	**.008**	**.284**	.111	.725
Asthma self-perception			**.000**			
Partially controlled	-2.821	.371	**.000**	**.060**	.029	.123
Uncontrolled	-20.921	5717.49	.997	**.000**	.000	-

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Table 4. Multivariate analysis of factors related to relief medication use

	B	E.T.	Sig.	Exp(B)	95% CI	
					Low	High
Smoking habit (reference: Non smoker)			**0.005**			
Smoker	1.426	0.482	**0.003**	4.160	1.618	10.699
Former smoker	0.810	0.360	**0.024**	2.248	1.111	4.548
Number of night awakenings	0.301	0.067	**0.000**	1.351	1.186	1.539
Asthma self perception			**0.000**			
Partially controlled	1.084	0.404	**0.007**	2.955	1.338	6.528
Un controlled	2.655	0.576	**0.000**	14.226	4.598	44.010
Questionnaire ACQ5	-1.330	0.482	**0.006**	0.264	0.103	0.680

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Figure legends

Figure 1. TAI profiles and use of relief medication

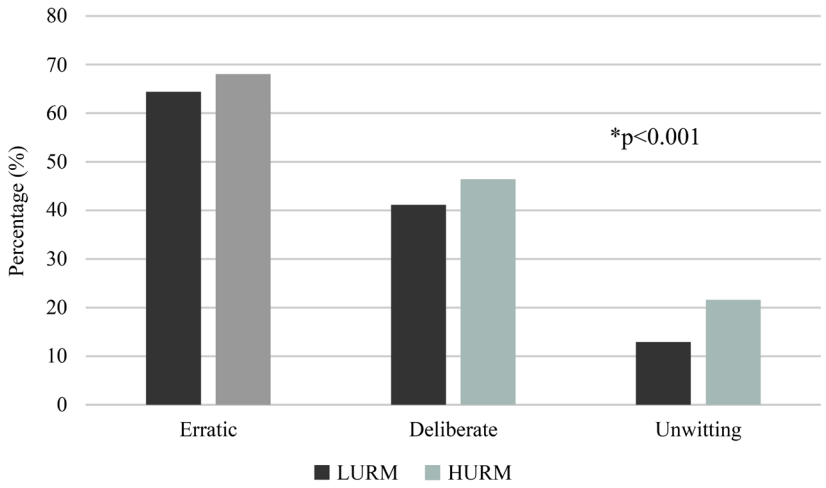
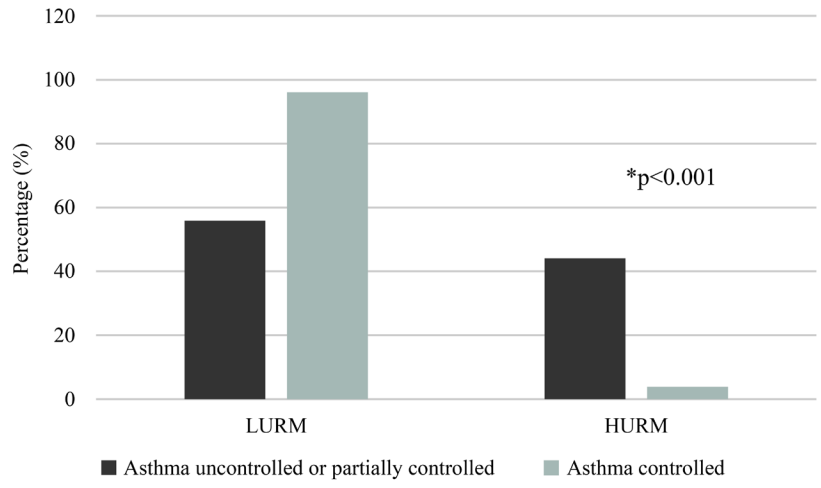


Figure 2: Asthma control and use of relief medication



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