

# Relevance of dosage in adherence to treatment with long-acting anticholinergics in patients with COPD

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**Introduction:** The aim of this study was to assess the degree of adherence for two standard regimens for administering anticholinergic drugs (12 and 24 hours) in patients with chronic obstruction of the airflow and to establish whether the use of a once-daily dose improves the level of treatment adherence.

**Methods:** We used long-acting anticholinergics (LAMAs) as a study variable, and included the entire health area of Castile-La Mancha, numbering 2,100,998 inhabitants, as the study population. We analyzed a total of 16,446 patients who had been prescribed a LAMA between January 1, 2013 and December 31, 2013. The follow-up period, based on a centralized system of electronic prescription management, was extended until December 2014.

**Results:** During 2013, the medication collected was 7.4%–10.7% higher than indicated by labeling. This was very similar for all LAMAs, irrespective of the patient's sex, the molecule, the device, and the drug dosage. We did not observe seasonal variations in the consumption of LAMAs, nor did we detect differences between prescription drugs for once-daily (every 24 hours) versus twice-daily (every 12 hours) administration, between the different molecules, or between different types of inhalers for the same molecule. The results were similar in 2014.

**Conclusion:** The principal conclusion of this study is that, in an area with a centralized management system of pharmacological prescriptions, adherence to treatment with LAMAs is very high, irrespective of the molecules or inhalation device. We did not find that patients who used twice-daily medication had a lower adherence.

**Keywords:** COPD, treatment, adherence, LABAs, LAMAs, PDC, asthma

## Introduction

The diseases that are accompanied by chronic obstruction of the airflow (chronic obstructive pulmonary disease (COPD) and severe persistent asthma) generate a major health care burden in most of the countries. Therefore, proper clinical management of the disease is of great importance not only for the patient but also for health systems. To achieve the best possible clinical management, there are a variety of clinical guidelines to aim at optimizing the treatment and reducing variability among professionals. These recommendations are frequently based on controlled clinical trials with results that may not always be extrapolated to real-life clinical practice. In addition to indicating the best treatment possible, an aim of our work was to determine the patient's adherence with treatment.

Patients with COPD or asthma, as well as other chronic diseases, frequently experience problems in adhering to treatment.<sup>1,2</sup> Poor adherence to treatment is one of the causes of poor clinical control, exacerbations, and hospitalizations and there

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are many factors related to this. George et al<sup>3</sup> identified some particularly important factors, such as the patient's level of knowledge about the disease and treatment, the doctor–patient relationship, administrative aspects, and the number of doses. With regard to the doses, an inverse relationship between the number of daily doses and the compliance rate has been reported.<sup>4</sup> If we exclude short-acting bronchodilators, whose indication in concordance with Global Initiative for Chronic Obstructive Lung Disease and Global Initiative for Asthma are only first-line therapy for those with minimal burden, most treatments are administered either every 12 or 24 hours. It has been claimed that administration every 24 hours could provide greater clinical benefit by improving adherence and, therefore, the efficacy of the treatment. This assumption is based on the observation that certain once-daily therapeutic regimens might lead to greater adherence compared with regimens requiring doses every 12 hours.<sup>5</sup> However, controversial results have been reported.<sup>6</sup>

Patients with COPD and severe persistent asthma have specific features and most present with persistent symptoms. Thus, it is unclear whether previous results, with other types of medication in other types of diseases, can be extrapolated to this population, and what administration regimen is best associated with good adherence by the patient. The aim of this study was to assess the degree of adherence with the two standard dosing regimens for long-acting anticholinergics (LAMAs) (every 12 and 24 hours) and to establish whether the use of a once-daily dose improves the level of treatment adherence.

## Materials and methods

For specific analysis of the impact of dosage on adherence to bronchodilator treatment in patients with chronic obstruction of the airflow, we evaluated the use of LAMAs as a study variable. The LAMAs currently exist on the market in 12- and 24-hour schedules and they have a good efficacy and safety profiles in all cases. Moreover, these drugs are exclusively indicated for patients with COPD and severe persistent asthma, who habitually have persistent symptoms. Therefore, in both cases, its use will be limited to patients who need them regularly, without seasonal changes. Long-acting beta-2 agonists (LABAs), alone or in combination with inhaled corticosteroids (ICs), were not included in the analysis because when assessed in large data bases it is impossible to properly differentiate whether the indication is for COPD or asthma and, in this case, whether it is a chronic or intermittent indication.

The study population was the entire health area of Castile-La Mancha, which included 2,100,998 registered inhabitants in January 2013, with 60% living in towns of

less than 20,000 residents. From this population, we selected all patients treated with a LAMA between January 1, 2013 and December 31, 2013. The initial sample included a total of 16,446 patients. The Castile-La Mancha Health Service has an electronic prescription system that enables the patient to be supervised and monitored, not only in terms of the doctor's instructions but also by collection of the drug from the pharmacy. This collection was specifically analyzed for all the LAMAs available on the market in 2013 (tiotropium [HandiHaler® and Respimat®], aclidinium, and glycopyrronium) on a monthly basis from January 1, 2013 to December 31, 2014. Aclidinium was available since January and glycopyrronium since April 2013. To obtain this information, we employed the Digitalis (The Castile-La Mancha Health Service [SESCAM], Toledo, Spain) application to analyze the information in medical prescriptions billed to the Castile-La Mancha Health Service.

The data are presented in absolute values and as a ratio between the number of doses collected by the patient at the pharmacy and the number of doses prescribed according to product labeling. Adherence was considered good when the ratio of the doses collected from the pharmacy and the number of days covered according to product labeling, or the proportion of days covered (PDC), was greater than 0.80.<sup>7</sup> For statistical analysis of qualitative variables, we used the  $\chi^2$  test.  $P < 0.05$  was considered significant. The study was authorized by local health authorities and approved by the Ethics Committee of Guadalajara Hospital. Patient consent was not required for this study as the information was obtained directly from a database without individual patient identification.

## Results

Initially, we assessed a total of 16,446 patients who had been prescribed a LAMA between January 1, 2013 and December 31, 2013. This group comprised 76.4% males, with an average age of 74.2 (standard deviation: 11.6) years, and 23.6% females with an average age of 74.2 (standard deviation: 13.6) years. The introduction of aclidinium and glycopyrronium in 2013 was responsible for the large differences in the number of prescriptions. In an overall analysis, we observed an excess in the collection of drugs in all cases. This was similar for all LAMAs, irrespective of the molecule, device, and drug dosage, with an average PDC greater than 1 in all cases (range: 1.074–1.107). Although most patients presented values very close to 1, a small percentage presented a ratio  $\geq 2$ ; 2% with aclidinium, 8% with glycopyrronium, and 9% with tiotropium (Table 1). The profiles for LAMA use were similar in males and females, without significant differences between sexes ( $\chi^2 = 2.91$ ;  $P = 0.23$ ).

**Table 1** Number of patients treated with LAMAs in 2013 and 2014, and PDC with a LAMA

	2013		2014	
	Patients	PDC	Patients	PDC
Tiotropium	15,252	1.10 (0.32)	11,946	1.09 (0.29)
Acclidinium	909	1.07 (0.29)	1,721	1.08 (0.27)
Glycopyrronium	285	1.07 (0.29)	1,388	1.08 (0.27)

**Note:** The standard deviation is given in parenthesis.

**Abbreviations:** LAMAs, long-acting anticholinergics; PDC, proportion of days covered.

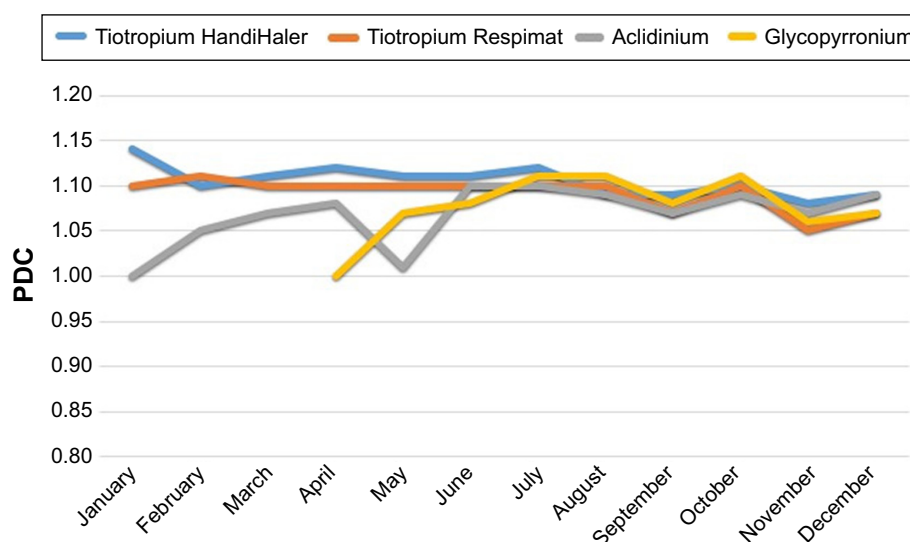
Although we choose LAMA because theoretically they do not have seasonal change, we wanted to confirm this assumption. To evaluate seasonal variations, we analyzed monthly use over the year. For all three molecules, irrespective of the device, we found greater use than indicated in the product labeling that fluctuated between 5% and 14%. We detected no relevant differences between the periods of the year, between the various prescription drugs dosed every 24 or 12 hours, or between the different types of inhalers for the same molecule (Figure 1). After the market introduction of acclidinium and glycopyrronium throughout 2013, we observed the same consumption profile for LAMAs in 2014, irrespective of variations in the molecule or device.

## Discussion

The principal conclusion of this study is that adherence to treatment with LAMAs is very high in an area with a centralized management system of drug prescriptions. There was consistently greater consumption (7.4%–10.7%) than indicated by the product labeling for all molecules and inhalation devices. We did not find that patients taking the

twice-daily dosage had a lower adherence to treatment. In a detailed analysis of the 2014 prescriptions, the percentage of patients with a ratio of 2 or greater was 2% with acclidinium, 8% with glycopyrronium, and 9% with tiotropium. Presumably, in some cases, the dose was taken more often than prescribed and there were losses of capsules with tiotropium and glycopyrronium, although the cause for this finding could not be firmly established.

Chronic respiratory diseases that require permanent use of maintenance therapy are often treated with LAMAs. For these treatments to be effective, appropriate adherence is necessary as improper use of these medications is a risk factor for mortality, morbidity, hospitalizations, and deterioration of quality of life.<sup>8,9</sup> In chronic diseases, the level of adherence to treatment fluctuates between 70% and 90% in clinical trials and between 10% and 40% in real-life clinical practice.<sup>10,11</sup> Two meta-analyses have assessed the relationship between the number of daily doses and the degree of treatment adherence, with higher adherence observed, from 7% to 23%, in the patients who took medication once a day compared with twice a day.<sup>12,13</sup> However, none of these studies specifically assessed patients with COPD and/or severe persistent asthma, whose common characteristic is the existence of persistent symptoms. In our series, with an initial population of 16,446 patients assessed on a monthly basis for 2 years, we found adherence to treatment with LAMAs to be optimal, ranging from 80% to 120% of the doses prescribed, a range that is accepted as good adherence in most clinical trials. Other series have analyzed different indices that assess the ratio of the days covered with the prescription and the treatment exposure time and established

**Figure 1** Monthly variation of PDC values during 2013 for tiotropium HandiHaler, tiotropium Respimat, acclidinium, and glycopyrronium.

**Abbreviation:** PDC, proportion of days covered.

that good adherence to treatment is when this quotient is higher than 0.80.<sup>7</sup>

In COPD patients, George et al<sup>3</sup> studied 30 variables related to adherence to treatment. They used a questionnaire but were only able to analyze 52.6% of the population selected. Although they identified a variety of factors related to the disease and the doctor–patient relationship, there was no specific analysis of the dosage or the type of drug. Bender et al<sup>14</sup> analyzed the adherence of the salmeterol–fluticasone combination and found PDC values to be ~22%. In our study, we deliberately did not analyze LABAs with ICs because the margin of error in the diagnosis of COPD and asthma was very high in large databases. In addition, the use of this medication in asthma is largely affected by its clinical characteristics and its severity, with patients with mild and moderate asthma not taking the medication in periods when they have no symptoms.<sup>15,16</sup> When analyzing LAMAs specifically, various authors reported that adherence to tiotropium was higher than ipratropium (four times a day), LABAs, and the LABA–IC combination.<sup>11</sup> Although these studies were conducted on COPD patients, they were not specifically designed to analyze the relationship between adherence and dose frequency. In a retrospective study, Toy et al,<sup>10</sup> in a sample of 55,076 patients with COPD, observed that adherence was related to dose frequency, with a PDC of 43.3% when it was administered once a day and 37%, 30.2%, and 23% when the frequency was four, three, and two times a day, respectively. However, this study evaluated mixes of different types of drugs (tiotropium, beta-2 agonists, LABA–IC, ipratropium); thus, multiple factors were associated with adherence, as well as the frequency of the doses, and this may have affected the results. An important aspect of adherence is its maintenance over time after the initial indication. In a series of 34,501 patients treated with statins, the degree of adherence with the treatment in elderly patients (average age: 74 years) fell over time, with the largest decrease taking place during the first 6 months.<sup>17</sup> In our series, the introduction of new molecules (aclidinium and glycopyrronium) presented a very stable profile during the period assessed and one that was very similar to tiotropium.

This study presents some specific features that should be taken into account. First, the results of this study are valid for LAMAs with standard indications in patients with persistent symptoms. Second, these results have been obtained in a public health system, where almost all funding of the medication have low expenses for the patients and monitoring of the prescriptions is done with a computerized system that communicates with all the pharmacies in the area of study.

The results could be different in other settings where the absence of controls and the high cost of medication may influence its regular use.<sup>18,19</sup>

The main limitation of this study is that we analyzed the drugs collected from the pharmacy, but did not confirm whether the patient really took the medication. However, this limitation may be extrapolated to most clinical trials, where adherence is assessed by counting the medication the patient returns and not by systems that really measure drug consumption. This work, which is based on data from a real-life clinical practice, includes a large study population with very consistent results irrespective of the period analyzed (January–December), the type of drug, or device. Therefore, we believe that it provides a true reflection of what is really occurring in our area. The second potential limitation is that we only analyzed LAMAs. However, we believe that this is a strength of the study because we removed misleading factors related to the therapeutic class and the type of condition involved. The use of LABAs and IC is frequent in patients with mild-to-moderate asthma, who may require varied treatment regimens during the year, with frequent abandonment of the medication in symptom-free periods. Finally, although LAMAs are specifically used to treat COPD patients, and to a lesser extent those with severe persistent asthma, we lack accurate spirometric confirmation since the computerized prescription management system does not enable precise analysis of the values of pulmonary function.

## Conclusion

Adherence to treatment with LAMAs is very high in patients diagnosed with COPD; in addition, the twice-daily dosage is not associated with lower treatment adherence.

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## Disclosure

The authors report no conflicts of interest in this work.

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