Drug Prescription for Chronic Obstructive Pulmonary Disease and Asthma by Primary Care Physicians in the Spanish Autonomous Community of Madrid, 1996-2002

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OBJECTIVE: To identify trends in the drug prescription used to treat chronic obstructive pulmonary disease (COPD) and asthma at the primary care level in Madrid between 1996 and 2002, and to assess the repercussion of new treatments.

PATIENTS AND METHODS: We analyzed information on primary care general practitioners' and pediatricians' drug prescription from the R03 group (drugs for obstructive airway diseases) of the Anatomical Therapeutic Chemical Classification System. Drug consumption was measured by recording the number of packages charged to the Spanish National Health Service and dispensed in pharmacies in the Spanish autonomous community of Madrid between 1999 and 2002. Consumption was expressed as defined daily dose per 1000 inhabitants per day.

RESULTS: Drug use expressed as defined daily dose per 1000 inhabitants per day for COPD and asthma in Madrid increased by 18.48% between 1996 and 2002. The use of adrenergic agonists, anticholinergics, and combinations of fixed doses of long acting β2 agonists with corticosteroids increased by 18.48% between 1996 and 2002. The use of β2 adrenergic agonist inhalants increased by 33.5% over the same period. The most marked differences were the increase in the number of patients treated with selective β2 adrenergic agonists, anticholinergics, and combinations of fixed doses of long acting β2 agonists with corticosteroids. The most-used drugs in 2002 were selective β2 adrenergic agonist inhalants (37.7%), anticholinergics (22.5%), corticosteroids (19.5%), and combinations of fixed doses of long acting β2 adrenergic agonists with corticosteroids (18.5%), and xanthines (5.03%). In 2002, the prescription of 5 new treatments amounted to 15.76% of total use of COPD and asthma drugs (R03 group).

CONCLUSIONS: Drug use for obstructive diseases of the airways showed a sharp increase between 1996 and 2002. Changes in patterns of use were observed, new treatments being quickly adopted, modifying the profile of drug prescription for the management of COPD and asthma.

Key words: Chronic Obstructive Pulmonary Disease (COPD). Asthma. Drug use. Defined daily dose. Primary care.

Utilización de medicamentos para la EPOC y el asma en atención primaria en la Comunidad de Madrid (1996-2002)

OBJETIVO: Conocer la tendencia en la utilización de los medicamentos para el tratamiento de la enfermedad pulmonar obstructiva crónica (EPOC) y el asma en atención primaria de Madrid entre 1996 y 2002, y evaluar la repercusión de las novedades terapéuticas.

PACIENTES Y MÉTODOS: Se ha analizado la información sobre el consumo, en número de envases, de los medicamentos incluidos en el grupo R03 (“Medicamentos para enfermedades obstructivas de las vías aéreas”) que prescribieron médicos de familia y pediatras de atención primaria, y que, facturados con cargo al Sistema Nacional de Salud, se dispensaron en las oficinas de farmacia de la Comunidad de Madrid en el período 1996-2002. El consumo se expresó en dosis diarias definidas por 1.000 habitantes y día.

RESULTADOS: El consumo de medicamentos, expresado en dosis diarias definidas por 1.000 habitantes y día, para la EPOC y el asma en Madrid aumentó un 18,48% entre 1996 y 2002. La utilización de la vía inhalada creció un 33,5% en dicho período. Las variaciones más destacables se centraron en el incremento del número de pacientes tratados con agonistas adrenérgicos β2 selectivos, anticolinérgicos y asociaciones a dosis fijas de agonistas β2 de acción larga con glucocorticoides. Los grupos más consumidos en 2002 fueron los agonistas adrenérgicos β2 selectivos por vía inhalada (37,7%), anticolinérgicos (22,5%), glucocorticoides (19,5%), asociaciones a dosis fijas de agonistas adrenérgicos β2 de acción larga junto con glucocorticoides (10,5%) y xantinas (5,03%). En 2002 la prescripción de 5 novedades terapéuticas generó el 15,76% del total del consumo de los fármacos utilizados en la EPOC y el asma (grupo R03).

CONCLUSIONES: El consumo de medicamentos para enfermedades obstructivas de las vías aéreas muestra un notable crecimiento entre 1996 y 2002. Se observan cambios en los patrones de utilización, incorporándose a gran velocidad nuevas opciones terapéuticas que modifican el perfil de prescripción de los medicamentos utilizados en el manejo de la EPOC y el asma.


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Introduction

Chronic obstructive pulmonary disease (COPD) and asthma are respiratory diseases of considerable importance due to their high morbidity and mortality rates and the considerable consumption of health care resources they generate.\(^1\) COPD is the respiratory disease with the greatest socioeconomic impact in Spain with a prevalence of about 9% that is expected to triple in 10 years.\(^2\) A study by Miravitlles et al.\(^3\) showed that this disease was responsible for 10% of primary care consultations and 35% of pneumology consultations. In 2001, 8,337 patients aged 30 years or older were hospitalized for COPD in Madrid. That figure represented 2.2% of the total hospital admissions for this population group.\(^4\) In monetary terms, it is estimated that pharmacotherapies for COPD range from 23% to 42% of the direct costs attributable to this disease,\(^5,6\) with a social and health care cost equivalent to 2% of the Spanish health care budget, or 0.25% of the gross national product.\(^7\)

The prevalence of asthma in the adult care population between 18 and 44 years in the autonomous community of Madrid was 4.8% in 2001.\(^8\) The figure was higher in the pediatric population and ranged from 5% to 11% in children from 7 to 14 years.\(^9,10\)

In economic terms, this disease generates consumption of between 1% and 2% of all public health care resources.\(^11\) It is estimated that about 50% of the total cost of the disease is attributable to direct costs, including drugs, medical staff salaries, visits to health care facilities, and particularly drugs, which can account for 45% of such costs according to Serra-Ballells et al.\(^12\)

The main objectives of the present study were as follows: 1) to describe trends in the consumption of drugs for the treatment of COPD and asthma financed by the National Health Service in the Spanish autonomous community of Madrid over a period of 7 years (from 1996 to 2002), 2) to describe changes in the pattern of use of the therapeutic subgroups and active agents included in the R03 group (drugs for obstructive airway diseases), and 3) to analyze the impact of the appearance of new drugs on the market.

Patients and Methods

We carried out a descriptive study in which we analyzed the prescribed drugs dispensed in pharmacies in the autonomous community of Madrid and charged to the National Health Service between 1996 and 2002. These drugs corresponded to prescriptions written on official medical prescription forms of the National Health Service by primary care physicians, both family doctors and pediatricians. Consumption of drugs prescribed by specialists, those generated by prescriptions of private physicians, and consumption of drugs without prescription were not included.

We evaluated all the drugs classified within the R03 therapeutic pharmacological subgroup (drugs for obstructive airway diseases) of the Anatomical Therapeutic Chemical Classification* (Table 1). We also included mepramine and ketotifen because they have been approved in Spain for use as antiasthmatic drugs.

Information on consumption was provided by the now defunct Madrid Institute of Health, aggregated according to national code of pharmaceutical specialties, broken down by health care areas of the autonomous community of Madrid, and expressed as number of packages.

Data were expressed as defined daily dose (DDD) per 1000 inhabitants per day. This parameter makes it possible to compare consumption expressed as mean daily maintenance doses for the main indication of each active agent for each route of administration in different geographic areas and at different times. The drug index (Nomenclátor) database of the Spanish Ministry of Health and Consumer Affairs dated December 2004 was used to calculate the number of DDD per package. Values not established in the drug index (Nomenclátor) were set in accordance with the regimens recommended in the literature. Conversion was carried out according to the following formula:

\[
\text{Number of DDD/1000 inhabitants/d} = \frac{\text{number of packages} \times \text{number of dosage units} \times \text{number of mg/U} \times 365 \text{days}}{\text{number of inhabitants}}
\]

\(1\)\(^2\) to analyze

TABLE 1

Drugs for Obstructive Airway Diseases in the R03 Therapeutic Group of the ATC*

<table>
<thead>
<tr>
<th>ATC Code</th>
<th>Therapeutic Subgroup</th>
<th>Active Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>R03AB</td>
<td>Nonselective (\beta) adrenergic agonists</td>
<td>Ocinoprenaline</td>
</tr>
<tr>
<td>R03AC</td>
<td>Selective (\beta) adrenergic agonists (inhaled)</td>
<td>Salbutamol, terbutaline, fenoterol, reprotofer, and procaterol</td>
</tr>
<tr>
<td>R03AH</td>
<td>Adrenergic combinations (antiasthmatic agents)</td>
<td>Isopenaline combined with other adrenergics</td>
</tr>
<tr>
<td>R03AK</td>
<td>Inhaled adrenergics combined with other antiasthmatic agents</td>
<td>Salbutamol + beclomethasone, salmeterol + fluticasone, formoterol + budesonide, salbutamol + ipratropium bromide, isopenaline + cromoglicic acid, isopenaline + phenylephrine, fenoterol + ipratropium bromide, and formoterol + budesonide</td>
</tr>
<tr>
<td>R03BA</td>
<td>Corticosteroids</td>
<td>Beclomethasone, budesonide, and fluticasone</td>
</tr>
<tr>
<td>R03BB</td>
<td>Anticholinergics</td>
<td>Ipratropium bromide</td>
</tr>
<tr>
<td>R03BC</td>
<td>(\alpha) and (\beta) adrenergic agonists (antiasthmatic agents)</td>
<td>Cromoglicic acid and nedocromil</td>
</tr>
<tr>
<td>R03CA</td>
<td>Systemic selective (\beta) adrenergic agonists</td>
<td>Ephedrine</td>
</tr>
<tr>
<td>R03DA</td>
<td>Xanthines (systemic antiasthmatic agents)</td>
<td>Theophylline, aminophylline, and theophylline</td>
</tr>
<tr>
<td>R03DD</td>
<td>Leukotriene receptor antagonists</td>
<td>Montelukast and zafirlukast</td>
</tr>
<tr>
<td>R03DC</td>
<td>Substituted ethylene diamines (antiasthmatics)</td>
<td>Mephenyline</td>
</tr>
<tr>
<td>R03DX</td>
<td>Other systemic antihistamines</td>
<td>Ketotifen</td>
</tr>
</tbody>
</table>

\*ATC indicates Anatomical Therapeutic Chemical Classification.
To calculate the number of inhabitants we used the figure published in the annual management contracts (Población Farmacia) of each health care area. This figure corresponds to the number of personal medical cards that entitle the bearer to pharmaceutical services.

Results

During the study period the use of drugs for COPD and asthma increased from 32.67 DDD/1000 inhabitants/d in 1996 to 38.67 DDD/1000 inhabitants/d in 2002. This represented an increase of 18.48%. This variation in consumption was not uniform throughout the 7 years of the study. Between 1996 and 2000 the use of drugs from the R03 group increased yearly, with an accumulated increase in DDD/1000 inhabitants/d of 24%, reaching a maximum in the year 2000 (40.57 DDD/1000 inhabitants/d). However, this trend was reversed between 2001 and 2002, when the number of DDD/1000 inhabitants/d decreased (Figure 1).

The pattern observed in the R03 group was mainly a reflection of what occurred in the case of inhaled drugs. For inhalants, the number of DDD/1000 inhabitants/d maintained an upward trend, with an increase in use from 26.3 DDD/1000 inhabitants/d in 1996 (80.57% of the total DDD/1000 inhabitants/d) to 35.09 DDD/1000 inhabitants/d (91% of the DDD/1000 inhabitants/d). This represented an increase of 10.18 DDD/1000 inhabitants/d (Figure 1).

It must be pointed out that this upward trend in the use of inhalants occurred only between the years 1996 and 2000, at which point it reached its maximum (36.01 DDD/1000 inhabitants/d), later decreasing by 2.55% until 2002. However, the use of drugs administered orally showed a tendency to decrease yearly between 1996 and 2002, decreasing from 6.32 DDD/1000 inhabitants/d in 1996 to 3.58 DDD/1000 inhabitants/d in 2002. This represented a decrease of 2.74 DDD/1000 inhabitants/d.

In the therapeutic subgroups with the highest consumption (Figure 2), the most marked differences were the increase in the number of patients treated with...
The consumption of anticholinergics (R03BB) doubled from 4.14 DDD/1000 inhabitants/d in 1996 to 8.69 DDD/1000 inhabitants/d in 2002, showing a tendency to increase over the 7 years of the study. The number of patients treated daily with selective inhaled adrenergics combined with other antiasthmatic agents (R03AK) also increased markedly from 0.74 DDD/1000 inhabitants/d in 1996 to 4.07 DDD/1000 inhabitants/d in 2002, reaching its maximum in 1999. The use of xanthines, however, decreased continually throughout the study period, from 5.25 DDD/1000 inhabitants/d in 1996 to 2.19 DDD/1000 inhabitants/d in 2002.

The use of drugs included in the therapeutic subgroups of inhaled β₂ adrenergic agonists (R03AC) and corticosteroids (R03BA), both as monotherapies, deserves special mention because it maintained an upward trend until the year 2000, decreasing in subsequent years. Leukotriene receptor antagonists (R03DC), introduced onto the Spanish market in 1998, gained market shares every year. In 2002, they were used by 0.75 patients of every 1000 treated with some medication for asthma or COPD.

The consumption of nedocromil and chromylcetic acid, included in the R03BC subgroup, as well as that of ketotifen (R06AX), showed a tendency to decrease throughout the study period.

As a consequence of these circumstances, the profile of drug prescription changed between 1996 and 2002. Noteworthy among these changes is that anticholinergics went from the fourth position in 1996 to the second position in 2002; combinations of β₂ agonists with antiasthmatic agents went from fifth position to fourth position, and xanthines from third position to fifth (Figure 2).

Analyzing consumption data by active agents, we observed that the 5 whose consumption increased between 1996 and 2002 were ipratropium bromide (4.55 DDD/1000 inhabitants/d), salmeterol plus fluticasone (2.33 DDD/1000 inhabitants/d), fluticasone (1.49 DDD/1000 inhabitants/d), formoterol (0.79 DDD/1000 inhabitants/d), and terbutaline (0.75 DDD/1000 inhabitants/d). The active agents whose consumption decreased the most were theophylline (–2.92 DDD/1000 inhabitants/d), beclomethasone (–1.30 DDD/1000 inhabitants/d), nedocromil (–0.55 DDD/1000 inhabitants/d), and budesonide (–0.45 DDD/1000 inhabitants/d) (Table 2).
In the specific case of active agents in the subgroup of inhaled selective \( \beta_2 \) adrenergic agonists (R03AC), which includes short-acting active agents usually associated with rescue medication (salbutamol and terbutaline) and long-acting active agents associated with maintenance medication (salmeterol and formoterol), the decrease in the number of DDD/1000 inhabitants/d was due mainly to the fall in consumption of salmeterol (Figure 3).

The profile of active agents changed considerably between 1996 and 2002. Those most used in 2002 were ipratropium bromide, inhaled salbutamol, budesonide, terbutaline, and salmeterol plus fluticasone (Figure 4).

### Table 3

<table>
<thead>
<tr>
<th>Year</th>
<th>Ipratropium Bromide</th>
<th>Terbutaline</th>
<th>Budesonide</th>
<th>Inhaled Salbutamol</th>
<th>Theophylline</th>
<th>Salmeterol</th>
<th>Fluticasone</th>
<th>Budesonide + Other Antiallergic Agents</th>
<th>Beclomethasone + Other Antiasthmatic Agents</th>
<th>Budesonide Combined With Other Antiasthmatic Agents</th>
<th>Fluticasone Combined With Other Antiasthmatic Agents</th>
<th>Total R03AC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
<td>22.40%</td>
<td>10.45%</td>
<td>19.28%</td>
<td>19.28%</td>
<td>3.67%</td>
<td>22.93%</td>
<td>19.28%</td>
<td>19.28%</td>
<td>19.28%</td>
<td>19.28%</td>
<td>19.28%</td>
<td>19.28%</td>
</tr>
<tr>
<td>2002</td>
<td>12.65%</td>
<td>10.22%</td>
<td>18.15%</td>
<td>19.28%</td>
<td>3.67%</td>
<td>14.12%</td>
<td>18.15%</td>
<td>19.28%</td>
<td>19.28%</td>
<td>19.28%</td>
<td>19.28%</td>
<td>19.28%</td>
</tr>
</tbody>
</table>

*NM indicates not marketed.
Between 1996 and 2002, 5 new treatments in the R03 group were introduced onto the market. Three of them were new active agents—fluticasone (1997), montelukast (1998), and zafirlukast (1999)—and 2 corresponded to combinations of already existing drugs—salmeterol plus fluticasone (2000) and formoterol plus budesonide (2001). These new therapies accounted for 15.76% of the total number of DDD/1000 inhabitants/d consumed.

Consumption of combinations of salmeterol plus fluticasone and of formoterol plus budesonide increased by 356.6% from its introduction onto the market and accounted for 91.9% of the total consumption of the R03AK subgroup in 2002. Fluticasone also had considerable impact on the therapeutic subgroup of corticosteroids (R03HA), as between 1997 and 2000 its consumption increased by as much as 2340.0%; at that time its share reached 24.4% of the entire subgroup of corticosteroids, but beginning in 2010 consumption decreased, as did that of the rest of the subgroup, and it finally accounted for 21.1% of the total of corticosteroids prescribed in 2002 (Table 3). The consumption of montelukast increased by 353.3% in its 4 years on the market, and that of zafirlukast, 300.0% in 3 years. Montelukast was the most-used active agent of the subgroup of leukotriene receptor agonists, accounting for 49.5% of the total consumption of the subgroup in 2002.

Discussion

Prescription of drugs for COPD and asthma in the autonomous community of Madrid increased considerably between 1996 and 2002, with consumption in 2002 of 38.67 DDD/1000 inhabitants/d. This figure is lower than that reported by García del Pozo et al., who estimated it at 43.7 DDD/1000 inhabitants in 1998 for Spain as a whole. The number of patients receiving daily pharmacological treatment for asthma or COPD increased by 18.28% between 1996 and 2002. This increase in the consumption of drugs for obstructive airway diseases could be explained by an increase in the prevalence of these diseases. Although numerous international studies have been published showing an increase in the prevalence of COPD and asthma, there is no direct information available on changes in the prevalence rates in Spain that would make an overall analysis possible.

Another possible explanation for this increased consumption is that patients with COPD may be receiving treatment at earlier stages of the disease. The 1999 IBERPOC study showed that only 78.2% of patients with COPD had already been diagnosed, and thus only 49.3% of patients with severe COPD, 11.8% of patients with moderate COPD, and 10% of patients with mild COPD were receiving some type of treatment. The increase in the use of inhaled devices as the preferred route of administration for COPD and asthma medication is worthy of note. This fact indicates that prescription is adhering to the recommendations published in all the guidelines and consensus statements, both Spanish and international, on the effectiveness of inhalation, the route of choice for the management of these diseases.

In the period analyzed, the pattern of drug consumption underwent substantial modification due mainly to the introduction of new drugs onto the market. Between 2001 and 2002 the use of all active agents marketed as monotherapies fell. These were adrenergic agonists with a short half life (rescue bronchodilators) and those with a long half life (maintenance bronchodilators), as well as corticosteroids.

It was to be expected that the appearance on the market of combinations of fixed doses of long-acting β₂ adrenergic agonists with corticosteroids (salmeterol and fluticasone, and formoterol plus budesonide) would to a certain extent displace the consumption of the same active agents marketed as monotherapies, and this was confirmed in the present study. A similar situation had already been observed in other countries. These new fixed-dose combination devices may be more convenient for the patient, as replacing 2 devices by a single one improves portability; however, they are neither more effective nor safer than their separate components, and there is no evidence to indicate that such devices improve adherence to therapy.

Another noteworthy finding of the present study is that beginning in 2001 the number of patients treated with short-acting or rescue β₂ agonists decreased. This could mean that the use of fixed-dose combination devices allows improved control for patients, resulting in a decreased need for rescue medication. This situation should be considered with caution, as the evidence to date is inconclusive and we do not have sufficient data to affirm that patients treated with these new fixed-dose combination devices have better results than those treated with monotherapies.

The number of patients treated with ipratropium bromide, the only anticholinergic marketed in Spain until 2002, doubled from 4.14 patients per 1000 in 1996 to almost 9 in 2002. These figures coincide with those published in other studies, which confirm that ipratropium bromide is the drug most used in patients with stable COPD. Considering that the prevalence of COPD is directly linked to smoking, and that in the autonomous community of Madrid 34.6% of people between 18 and 64 years smoke on a daily basis, the consumption of anticholinergics in the coming years may be expected to show an upward trend similar to, or perhaps greater than, that observed in the present study. Given that anticholinergics are used almost exclusively in COPD, their consumption expressed as DDD/1000 inhabitants/d could be used as an indirect indicator of the magnitude of this health problem and gives some idea of the increase in the prevalence of this disease.

The continued decrease in the use of xanthines (theophylline and aminophylline) seems logical and desirable, given the problems of interactions and adverse effects associated with them, although their effectiveness has been amply demonstrated.

In the 2002 profile, as a consequence of the coming into effect of the Royal Decree on selective financing of 1998, we no longer see the marketing of fixed-dose combination devices of drugs with salbutamol or salmeterol plus ipratropium bromide (some as the combination of methylxanthines with corticosteroids and nonselective adrenergic agonists). By virtue of this administrative move, drugs with no therapeutic usefulness

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were excluded from funding and, as a result, the quality of drug prescription for these obstructive airway diseases improved.

With regard to new therapies, fluticasone, which appeared on the market in 1997, had very limited impact on the treatment of asthma, although no clinically significant benefits have been shown. From its appearance up to the year 2000, it progressively gained market shares, although it never managed to displace budesonide as the inhaled corticosteroid of choice. Its use was a monotherapy was slowed only after the combination of this same corticosteroid with salmeterol, which displaced it to some extent. The use of a fixed-dose combination of β₂ agonists with corticosteroids (fluticasone plus salmeterol) increased considerably as soon as it appeared on the market, displacing part of the consumption of both active agents as monotherapies. Other new treatments launched in the Spanish market between 1998 and 1999 were leukotriene receptor antagonists, with an indication limited to the treatment of asthma. Consumption of these drugs was relatively low, but greater than was to be expected in view of the fact that their effectiveness in the treatment of asthma is very limited. In fact, in 2002 they were the sixth most-used therapeutic subgroup, displacing chromones (cromolglicic acid and nedocromil) from this position.

In order to interpret the findings of this study properly, certain limitations need to be taken into consideration. The most important of these is that the source of information on drug prescription did not take into account prescription of drugs generated by agencies within the Spanish national health care system that manage plans for specific groups, such as MUFACE (civil servants), ISFAS (armed forces), etc. Nor did this study include prescriptions by physicians in private practice or self-medication. Consequently, our data underestimate the real use of drugs for asthma and COPD in Madrid. Furthermore, in this study we have expressed data on consumption as DDD/1000 inhabitants/d, following the recommendations of the World Health Organization and using the drug index (Nomenclátor) of the Spanish Ministry of Health as a database. It must be remembered that the DDD need not coincide with the actual dose used by the population, although it is a good approximation of the consumption expressed as DDD/1000 inhabitants/d. The increase in the use of inhalants and the elimination of prescriptions of doubtful efficacy or safety are signs of a more rational use of drugs. Moreover, new therapeutic options have been incorporated at great speed and they have had considerable impact on the management of the 2 diseases. They have managed to displace other drugs of proved efficacy, although to date their health benefits, and the clinical significance of such benefits, have not been demonstrated.

REFERENCES


