

## TRENDS IN PHARMACOTHERAPY FOR CHRONIC AIRFLOW LIMITATION IN ARGENTINA: 1992-2002

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**Abstract** Asthma and COPD mortality rates have decreased in Argentina. These trends might be the result of the way these conditions are being treated. The number of units for prescription and over-the-counter (OTC) drugs used to treat chronic airflow limitation in Argentina from 1992 through 2002 were analyzed. Units for drugs to treat chronic airflow limitation fell by 45% over the 11-year period ( $p < 0.0001$ ) due to significant reductions for oral  $\beta_2$ -agonists (OBA) (down 73%), theophyllines (down 74%), oral steroids (OS) (down 66%) and inhaled short-acting  $\beta_2$ -agonists (ISABA) (down 28%). Market share for inhaled steroids (IS) increased from 2.6% to 11.7%, for inhaled ipratropium (IP) from 0.35% to 3.7%, for the combination of inhaled steroids with short-acting  $\beta_2$ -agonists (IS+ISABA) from 7.8% to 13%, and for inhaled IP combined with short-acting  $\beta_2$ -agonists (IP+ISABA) it increased from 1.7% to 7.3%. Inhaled long-acting  $\beta_2$ -agonists (LABA) and leukotriene modifiers (LM) were rarely prescribed. The use of more specific inhaled therapies (IS, IP) increased significantly in accordance with recommendations for the treatment of asthma and COPD and this may explain the reduction in asthma and COPD mortality in Argentina.

**Key words:** COPD, asthma, bronchodilators, inhaled steroids, morbidity, mortality, pharmacoconomics

**Resumen** *Tendencias en el tratamiento farmacológico de la obstrucción crónica al flujo aéreo en Argentina: 1992-2002.* Las tasas de mortalidad por asma y enfermedad pulmonar obstructiva crónica (EPOC) se han reducido en Argentina. Estas tendencias pueden deberse a la forma en que tales enfermedades son tratadas. Se analizaron los medicamentos utilizados para el tratamiento del asma y EPOC desde 1992 hasta el año 2002. El total de unidades utilizadas cayó un 45% ( $p = 0.0001$ ) debido a una reducción significativa de los agonistas orales  $\beta_2$  (83%), las teofilinas (74%) los esteroides orales (66%) y los agonistas inhalados  $\beta_2$  de acción corta (28%). La fracción de mercado de los esteroides inhalados aumentó del 2.6% al 11.7%, en el caso de ipratropio del 0.35% al 3.7%, la combinación de esteroides inhalados y agonistas  $\beta_2$  de acción corta aumentaron del 7.8% al 13% y la combinación de ipratropio con agonistas inhalados  $\beta_2$  de acción corta aumentó del 1.7% al 7.3%. Los agonistas inhalados  $\beta_2$  de acción prolongada y los antileukotrienos fueron recetados raramente en el período analizado. El uso de terapias más específicas (esteroides inhalados e ipratropio) aumentó significativamente de acuerdo con las recomendaciones para el tratamiento del asma y EPOC y esto podría explicar las reducciones en las tasas de mortalidad de estas enfermedades.

**Palabras clave:** EPOC, asma, broncodilatadores, esteroides inhalados, mortalidad

Disparate trends in 18-year mortality rates (i.e. reduction in mortality due to asthma and increase in mortality due to COPD) have been reported in Argentina<sup>1</sup>. More recently, COPD mortality has curved down and whether this is related, at least partially, to changes in the prescribing patterns of drugs used to treat chronic airflow limitation is unknown<sup>2</sup>.

Prescribing trends of drugs to treat chronic airflow limitation from 1983-1990 in Argentina have been previously reported<sup>3</sup>. During this period, an increased use of ISABA, trends away from the use of oral theophyllines (OT) and away from oral  $\beta_2$ -agonists (OBA) were found, and IS were

rarely used (1.9% of all prescriptions in 1990)<sup>3</sup>. We hypothesized that many patients with chronic airflow limitation, particularly asthmatics, were being sub-optimally treated with IS, which might have resulted in increasing asthma morbidity and mortality in the 1980s in Argentina<sup>1,3</sup>.

In order to generate the hypothesis that the steady decline in asthma mortality in Argentina in the 1990s<sup>1</sup> and the more recent decline in COPD mortality may be associated to changes in the therapeutic management of these conditions, the quarterly volume of dispensed units for drugs used in the treatment of chronic airflow limitation in Argentina during the period from 1992 to 2003 were analyzed.

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**Material and Methods**

Data collected from wholesalers and pharmacies in Argentina were obtained from *IMS MIDAS* and analyzed on a quar-

terly basis. *IMS MIDAS* (from *IMS Health*) assesses worldwide healthcare markets. It accurately details estimated product volumes, trends and market share by product and therapy class through retail and non-retail channels. The data analyzed in this report included both prescribed and over-the-counter (OTC) medications used to treat chronic airflow limitation.

Although we have previously reported data from 1983 to 1990<sup>3</sup>, no data for 1991 could be obtained; thus, the current analysis begins in 1992. Data from 11 complete years (1992 to 2002 inclusive) and for Qtr1 and Qtr2 of 2003 were available for analysis.

For the purpose of the analysis, the drugs to treat airflow limitation were divided into 8 main categories (Table 1):  $\beta_2$ -agonists (oral, short-acting and long-acting), corticosteroids (oral and inhaled), oral theophyllines, ipratropium, anti-histamines and leukotriene modifiers. The combinations of IS or IP with ISABA were analyzed separately.

Least square linear regression was used to assess changes in prescriptions of sales from Qtr1 1992 to Qtr4 2002 for each category. T-test was used to assess changes in volume of drugs dispensed in the different seasons. Changes were considered significant at the level  $< 0.05$ . SAS version 8.2 was used for the analyses.

## Results

From Qtr1 1992 to Qtr4 2002 sales decreased significantly ( $p < 0.0001$ ; Fig. 1; Table 1). There was a significant decrease in the volume of oral compounds such as  $\beta_2$ -agonists, corticosteroids and theophyllines; ( $p < 0.0001$ ; Fig. 2). Short-acting inhaled  $\beta_2$ -agonists were the most frequently used drugs, yet units for these decreased by 28% during the 11-year period ( $p < 0.001$ ; Fig. 3). Medications that showed an increase in unit volume were inhaled steroids and inhaled ipratropium, either alone or in combination with short-acting  $\beta_2$ -agonists ( $p < 0.0001$ ;

Fig. 4). Inhaled ipratropium increased more (8-fold) than other inhaled compounds, yet still comprised only 3.7% of all units in 2002 (Table 1). Units of inhaled steroids, both alone and in combination with short-acting  $\beta_2$ -agonists, comprised nearly 25% of the market in 2002 as compared to 10.4% of the 1992 market while the compounds containing ipratropium comprised 1.9% of all units in 1992 and 11% in 2002 (Table 1).

All medications showed marked seasonal variations in unit volume, which were highest ( $p < 0.0001$ ) every year during the autumn and winter (Figs. 1 to 4). In 2002 the use of all drugs was further reduced ( $p < 0.02$ ; Fig. 1) to unprecedented low levels.

## Discussion

This report shows that the number of units for drugs to treat airflow limitation has fallen steadily in the period from 1992 to 2002, with a sharp decline during 2002 (Fig. 1). In this 11-year period, units of oral compounds (Fig. 2) and units of inhaled short-acting  $\beta_2$ -agonists (Fig. 3) decreased while inhaled steroids and inhaled ipratropium have increased (Fig. 4). The increases in the use of IP combined with inhaled short-acting  $\beta_2$ -agonists partially replaced inhaled short-acting  $\beta_2$ -agonists (Figs. 3, 4 and Table 1).

Drug sales data do not substantiate hypotheses but can only serve to generate them. In this regard, given that mortality due to asthma has fallen steadily in Argentina<sup>1</sup>, and assuming that inhaled steroids were used primarily by asthmatics, one can hypothesize that the fall in

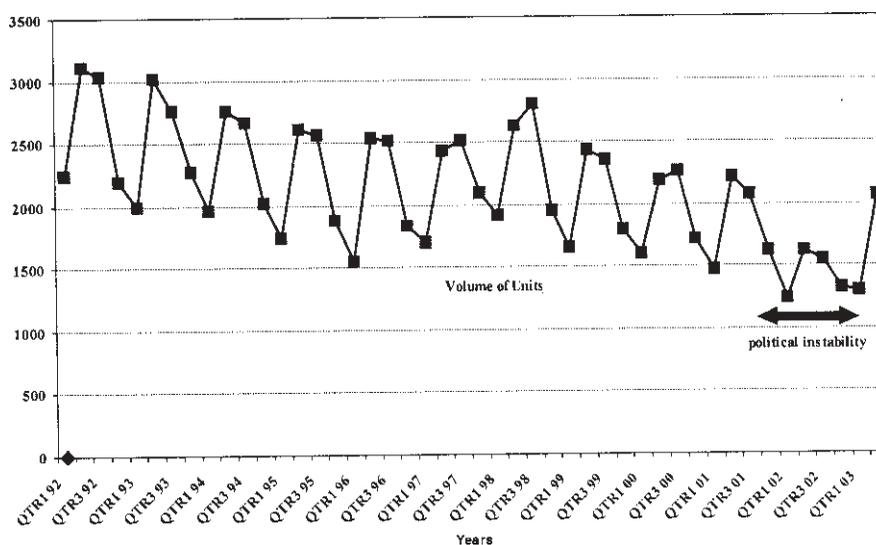


Fig. 1.— Dispensed units of all medications decreased significantly ( $p < 0.0001$ ). Further significant falls were seen during 2002 due to socioeconomic and political instability ( $p < 0.02$ ). Qtr: quatrimester. Autumn and winter comprise Qtr 2 and Qtr 3 of each year (Southern Hemisphere).

TABLE 1.- An 11-year comparison of total units dispensed and percent share of the respiratory market in Argentina (1992-2002 inclusive)

	1992		2002		Change from baseline in %
	Units in thousands	Market share %	Units in thousands	Market share %	
ALL	10.574	100	5.747	100	- 45**
Short-acting $\beta_2$ -agonists	3.575	33.8	2570	44.7	- 28*
Oral $\beta_2$ -agonists	1.440	13.6	240	4.2	- 83**
Inh. long-acting $\beta_2$ -agonists*	22	0.2	82	1.4	+ 272**
Inh. steroids	283	2.6	676	11.7	+ 138**
Inh. steroids + $\beta_2$ -agonists	829	7.8	745	13	- 10 (NS)
Oral steroids	193	1.8	43	0.7	- 77**
Ipratropium	23	0.2	217	3.7	+ 843**
Ipratropium + $\beta_2$ -agonists	185	1.7	424	7.3	+ 129**
Oral theophyllines	2696	25.5	460	8	- 83**
Leukotriene modifiers*	0	0	63	1.1	NA
Anti-histaminics	1.108	10.4	183	3.2	- 83**

Legend: ♣ = launched in Qtr3 1992; ♦ = launched in Qtr4 1997; NS = non-significant; \* :  $p < 0.001$ ; \*\* :  $p < 0.0001$

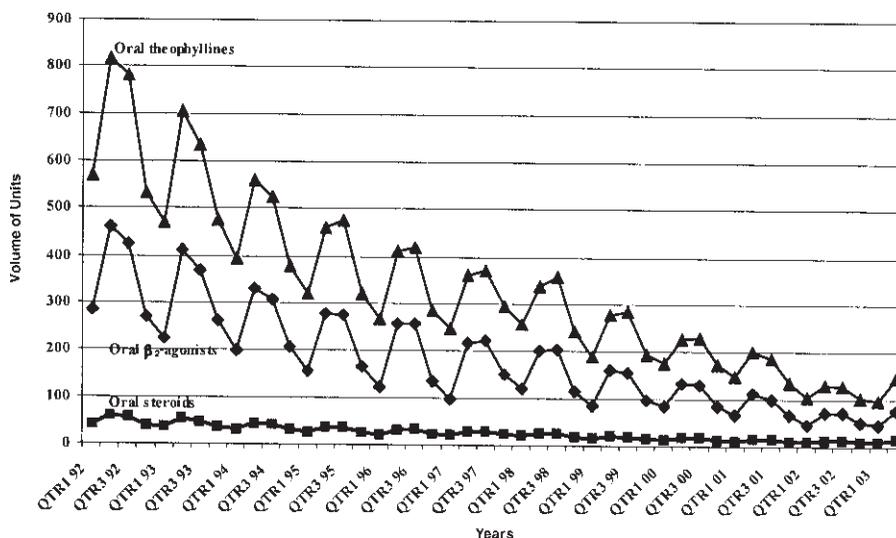


Fig. 2.- Significant decrease of dispensed units of oral compounds ( $p < 0.0001$ ).

mortality is due to increased usage of inhaled steroids. This has been reported in other parts of the world<sup>2</sup>. In addition, after steady increase for 18 years, mortality due to COPD in Argentina has now fallen from 27.2/100 000 in 1998<sup>1</sup>, to 26.6/100 000 in 1999, and further to 22.7/100 000 in 2000 (Sívori, Pacansky and Saenz). Furthermore, the decline in the usage of oral steroids, which are used to treat asthma<sup>4</sup> and COPD exacerbations<sup>5</sup> and are prescribed in post-exacerbation periods<sup>6, 7</sup>, may be in-

dicative of less morbidity due to asthma and COPD. From this report it is difficult to ascertain if the reduction in use of ISABA led to less asthma and COPD mortality<sup>2</sup> or if the better control of such conditions by more specific agents (IS and IP) led to a decrease in the use of ISABA (not counterbalanced by the increase in use of IP + ISABA; Table 1).

One major limitation of this report is the assumption that all drugs were either prescribed or obtained OTC to

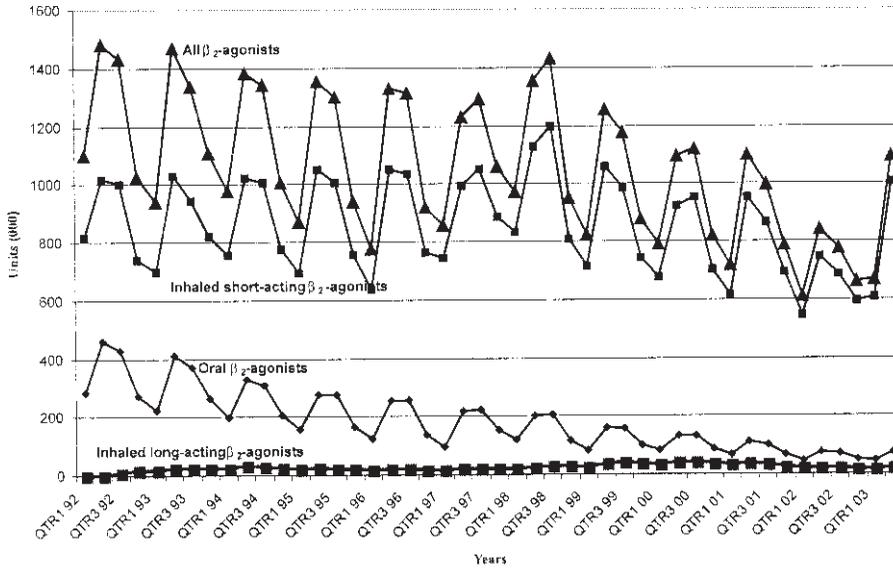


Fig 3.— Of all  $\beta_2$ -agonists used, greater proportion corresponds to inhaled short-acting  $\beta_2$ -agonists that fell by 28% in the 11-year period ( $p < 0.001$ ).

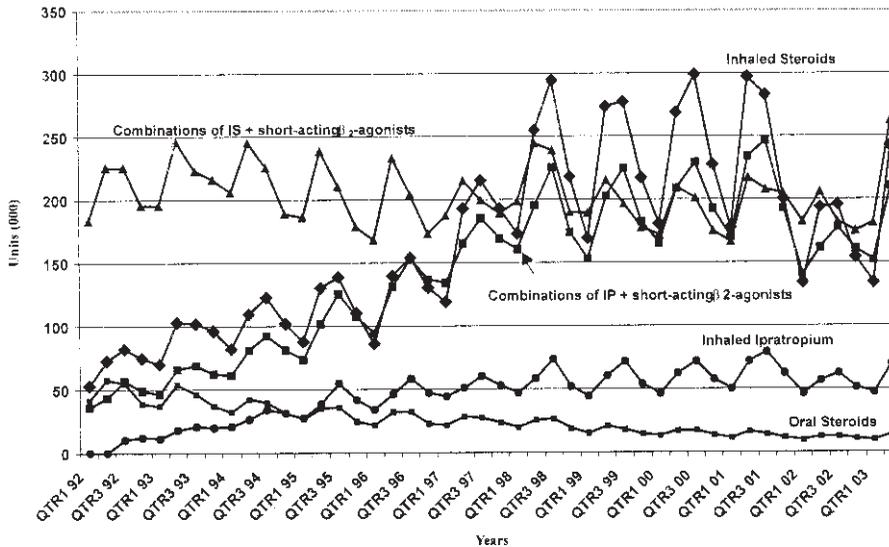


Fig. 4.— Significant increase of inhaled steroids and ipratropium as monodrugs ( $p < 0.0001$ ) as well as increase of the combination of inhaled ipratropium with inhaled short-acting  $\beta_2$ -agonists ( $p < 0.0001$ ). Stabilization of the combination inhaled steroids with inhaled short-acting  $\beta_2$ -agonists (10% fall = NS). Significant decrease is seen in the use of oral steroids ( $p < 0.0001$ ).

treat asthma and COPD and that the drugs were actually used by the patients. However, in light of the national and international guidelines for the treatment of such conditions that were used in the 1990s<sup>8,9</sup> in Argentina, it is very likely that asthma and COPD were the major conditions being treated by the therapies described in this report.

Concerns have been raised about the hypothesis that inhaled ipratropium usage may be related to excess deaths in COPD subjects<sup>10</sup>. Although this has been debated<sup>11</sup>, the issue is far from solved<sup>12</sup> and it is unknown if any extrapolation can be made to the new long-acting anticholinergic, tiotropium. However, this report shows that IP comprised only 11% of the 2002 market. Indeed,

despite the increased prescribing of ipratropium alone or in combination with short-acting  $\beta_2$ -agonists, COPD mortality has fallen and the rate of 22.7/100 000 in 2000 is currently lower than in the USA<sup>13</sup>. Whether this recent reduction in COPD mortality can be the effect of IS usage by COPD patients is unknown at the moment. However, although inhaled steroids have been shown to reduce acute exacerbations in COPD patients who exhibit an FEV<sub>1</sub> < 50% of predicted<sup>14</sup>, previous observational reports on reduction of mortality<sup>15, 16</sup> seemed flawed by immortal time bias<sup>17</sup> and avoiding this bias have yielded no effect of IS on COPD mortality<sup>18</sup>. In brief, after hospitalization a patient must survive to receive IS, and this time elapsed (called immortal time) between discharge and prescription of IS was unaccounted for in previous studies, resulting in an artificially high death rate in the control groups (unexposed to IS) creating a bias in favor of IS. The patients were prescribed short-acting  $\beta_2$ -agonists after discharge and they were switched to salmeterol or inhaled fluticasone. Yet, only those surviving (immortal) could switch to IS creating an effectiveness bias. Thus, whether IS would impact COPD mortality is being prospectively explored presently<sup>19</sup>.

Similarly, whether the reduction of COPD mortality since 1998 in Argentina is the result of greater use of ipratropium is unknown, and large studies are currently underway to assess any disease-modifying effect that inhaled anticholinergics, tiotropium specifically, may have.

Long acting  $\beta_2$ -agonists and leukotriene modifiers were rarely used (less than 2% of the market at their peaks) which is at odds with trends observed in other countries<sup>20, 21</sup>. Reasons for this may be the price of such compounds, late introduction into the market, and absence of recommendations by local treatment Guidelines<sup>8, 9</sup>. An effect of these drugs on the mortality trends for asthma or COPD in Argentina, if any, seems unlikely.

Nonetheless, the continuing smoking habit of the population<sup>22</sup>, the lack of appropriate therapies to deter the relentless progression of COPD, and the difficulty in accessing medical care in many cases, are the major causes of COPD morbidity and mortality in Argentina. In addition, the significant and consistent increases in dispensed units seen every winter season in Argentina suggest asthma and COPD deteriorated likely due to upper respiratory tract infections<sup>23, 24</sup>. Seasonal exacerbations of asthma are known to occur in Argentina and elsewhere when sudden drops of temperature, humidity and pressure occur<sup>25</sup>. More hospital admissions due to COPD exacerbations also occur in the winter<sup>23, 24, 26</sup>, but this phenomenon has not been previously reported in Argentina. Lastly, the significant drop in drug utilization because of economic hardships imposed by socioeconomic and political instability during the period from 2001 to 2003<sup>27</sup> may have resulted in a large proportion of untreated patients, including those with airflow obstruction<sup>28</sup>, and

whether this translated into a peak of excess morbidity and mortality during the winter of 2002 warrants further research.

In conclusion, trends in utilization of drugs to treat chronic airflow limitation suggest that decreased use of oral compounds and of inhaled short-acting  $\beta_2$ -agonists and increased use of IS and IP are associated with less asthma mortality and with a trend downwards in COPD mortality for the first time in Argentina.

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**141.** No escucharse. Poco aprovecha agradarse a sí, sino contenta a los demás, y de ordinario castiga e desprecio común la satisfacción particular; débese a todos el que se paga de sí mismo, querer hablar, y oírse no sale bien; y si hablarse a solas, es locura escucharse delante de otros, será doblada. Achaque de señores es hablar con el bordón, del digo algo, y aquel que aporrea a los que escuchan; a cada razón orejea la aprobación, o la lisonja, apurando la cordura. También los hinchados hablan con Eco, y como su conversación va en chapines de entono, a cada palabra solicita el enfadoso socorro del necio, bien dicho.

[Baltasar] Lorenzo Gracián (1601-1658)

*Oráculo Manual y Arte de Prudencia* (1647). Impresión facsimilar de la edición príncipe (Huesca) por Jorge M. Furt. Buenos Aires: Coni, 1958. Con ligeras modificaciones de la ortografía.