

Policies to enhance the efficiency of prescribing in the Spanish Catalan region: impact and future direction

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Aim: To assess the impact of recent national and regional initiatives on the utilization and expenditure of four high-volume classes to provide future guidance. These were proton pump inhibitors, statins and ezetimibe, and renin–angiotensin drugs, as well as newer antidepressants.

Methods: An observational study of prescriptions dispensed in ambulatory care in Catalonia was conducted from 2003 to 2007. Utilization was converted into defined daily doses (DDDs) and DDDs per 1000 inhabitants per day, and compared over the study period, as well as with other European countries. **Results:** As expected, there was increasing utilization of statins and renin–angiotensin drugs during the study period, as well as increased utilization of generics versus originators in each class; the latter figures were substantially greater than those published previously. There was also increased utilization of the proton pump inhibitors, which is a cause for concern. There were substantial reductions in the expenditure/DDDs of generics and originator products in 2007 versus 2003. For instance, expenditure/DDDs of generic and originator simvastatin were 81 and 72%, respectively, below 2003 originator prices. These reductions were much greater than those seen in previous publications. The increased utilization of generics, coupled with lower expenditure/DDDs for the classes, led to reduced reimbursed expenditure for the proton pump inhibitors, statins and newer antidepressants over time.

Conclusion: The findings are in line with expectations and do provide direction to other European countries, especially those with higher expenditures/DDDs for generics. There is an opportunity for Catalonia to learn from other countries to further enhance the quality and efficiency of its prescribing, and possible initiatives are discussed.

KEYWORDS: drug costs and expenditure • drug utilization • generics • pharmaceuticals • reforms • Spain

There is now complete decentralization of expenditure and clinical care to the autonomous communities (regions) in Spain [1,101]. In Catalonia, the Catalan Department of Health has instigated a number of initiatives over the years to try and improve the health of its population of 7 million inhabitants, as well as generally enhance the quality and efficiency of care. Ambulatory care is well developed in Spain through primary healthcare centers (PHCs), with each PHC providing general medical and pharmaceutical care, as well as a broad range of other services [102]. Physicians in PHCs also have an active gatekeeper role, restricting access to specialized services to help optimize the use of resources [102]. PHCs are largely publicly financed in Spain and are mainly managed

by public services in the regions (autonomous communities). However, in Catalonia, PHCs may be managed by both public and private institutions [102] with incentives to achieve agreed goals and penalties for budget deficits. Overall, in Catalonia, approximately 25% of PHCs are privately managed. Both the quality and efficiency of care is maintained among the privately run PHCs through close scrutiny of agreed targets. This includes targets for the prescribing of selected products in a class, as well as public health targets, waiting list targets and targets for disseminating information to patients. Efficiency in this context means prescribing the cheapest formulation when multiple sources exist with the same efficacy, as well as generics first line in a class where these are seen

Table 1. National initiatives to moderate pharmaceutical expenditure in Spain in recent years, including reference pricing initiatives.

Year	Reference pricing initiatives			Price cuts
	Homogeneous groups introduced (n)	Chemical entities (n)	Potential for additional copayment for a more expensive product	
2000	114	42	Yes	Yes
2001	28	17	Yes	Yes
2002	39	19	Yes	No
2003	82	62	No	No
2004	12	10	No	Yes
2005	0	0	No	Yes
2006	136	119	No	Yes
2007	14	14	No	No

Price cuts can be for all or some products. They also include reduced fees to wholesalers and community pharmacists. Homogenous groups contain all drugs with identical bioequivalent chemical entities in the same pharmaceutical form, dose and administration route, and must include at least one generic product.

as the standard versus more expensive single-sourced products. This includes prescribing generic omeprazole prior to esomeprazole and generic simvastatin first line before more expensive single-sourced statins [2].

The various initiatives to improve the health of the population have been developed by health providers together with the Catalan Health Service, the entity responsible for funding, planning and contracting healthcare in Catalonia [101]. Pharmaceutical expenditure has been the main component increasing healthcare costs in Spain in recent years [102,103], rising when combined with other nonmedical durables from 17.8% of overall healthcare expenditure (in 1990) to 23.2% (in 2005) before falling to 21% (in 2007) [104]. The rate of increase in pharmaceutical expenditure in the 1990s and early 2000s was difficult to sustain if the regions, including Catalonia, wished to continue providing comprehensive and equitable healthcare without prohibitive increases in national and regional taxes. As a result, a variety of national and regional reforms and initiatives were introduced in Spain in the early 2000s to try and moderate pharmaceutical expenditure. These centered on the two components driving expenditure: prices and prescribing volumes [2,3,102,105–108].

The various national and regional reforms and initiatives included compulsory price cuts, reference pricing for homogeneous molecules [1,4–6,102], as well as guidelines, drug information bulletins and quality-of-care indicators linked with financial incentives [106–108]; the latter, for instance, helping to enhance the prescribing of generics in a class. Pricing policies, including those for generics, are established centrally in Spain. Initiatives to influence prescribing are typically instigated by the autonomous communities following the decentralization of budgets, including the drug budget [1,102,103].

The reference pricing system in Spain is different to other European countries as it works as a maximum price system for the drugs included within homogeneous groups [1]. Homogeneous groups contain the same chemical entity, dose and route of administration and must contain at least one generic [1]. Under this system,

patients do not have the option of paying any price difference themselves between the reference price and a preferred brand [1], which is different to most other European countries [2,7,105]. In addition, for new generics to be reimbursed, they must have a price equal to or lower than the current reference price [1]. TABLE 1 contains details of pricing policies introduced centrally from 2000 to 2007. The reference pricing system was widened in 2003 following its introduction in 1999 where 114 homogeneous groups were initially created [1]. After 2003, there is no potential for an additional copayment for more expensive products than the current reference price. The intention of this is to increase the prescribing and dispensing of generics, as well as lower their prices. The law further states that if the retail price of a prescribed drug (whether an originator or a

generic) is equal to or lower than the reference price, the pharmacist should not substitute the prescription for a generic [1]. However, from 2007, to help engineer further price reductions, substitution with the cheapest product dispensed was made mandatory if the price of the prescribed product was higher than the current reference price [1,4,102,105]. This would be the generic drug if the cheapest retail price of the generic and brand drugs are priced equally [1].

The reference price for each homogeneous group is calculated by averaging the three current products with the lowest daily treatment cost based on defined daily doses (DDDs) [109]. In addition, a 2003 law established that the minimum threshold for the reference price for a pack should be €2 per month; this was increased to €3.12 in 2007 [1].

Pediatric formulations for given products were included in different homogeneous group, reflecting their different status. Innovative line extensions of products included in current homogeneous groups, as defined by the Ministry, are currently excluded from the reference price system and can still command a premium price; however, these will join the reference price groups after 5 years on the market [1]. As a result of these measures, pharmaceutical companies typically lowered the prices of originator products following patent loss, certainly initially, to try and maintain at least some market share.

Alongside national initiatives, a number of initiatives have been introduced in Catalonia in recent years to enhance the quality and efficiency of prescribing among the PHCs (TABLE 1). These have been categorized under the 4E approach, which has been used elsewhere to classify the different initiatives that influence behavior and now adapted to healthcare [2,8,9]. Some of the initiatives documented in BOX 1 were already in existence in 2003. Others have been gradually introduced across the region over the study period, with the rate of introduction varying locally. Consequently, it has been difficult to include these in a meaningful timeline, and they should be viewed as a continuum over the period of the study.

Box 1. Ongoing initiatives to improve the quality and efficiency of prescribing in Catalonia during the study period.**Education** [3,4,6,39,102,106,111,113,114,125–129]

- Benchmarking primary healthcare physician prescribing
- Academic detailing to enhance the prescribing of generics first line where seen as standard
- Production and dissemination of multidisciplinary guidelines on primary healthcare problems, including hypercholesterolemia, hypertension, diabetes, cardiac insufficiency and dyspepsia
- Production and dissemination of drug information bulletins
- Pharmacists and clinical pharmacologists providing information on therapeutics to primary healthcare physicians to improve the quality and efficiency of their prescribing
- Educational courses on primary healthcare problems

Engineering [108]

- Catalan Health Service contracts with providers incorporate quality-of-care indicators and quality-of-prescription indicators, including:
 - New drugs prescribed that have limited value over existing standards
 - Percent of oral antidiabetic prescriptions as metformin
- Primary healthcare centers may also instigate their own quality and efficiency measures to help attain financial incentives, including:
 - Percent of prescriptions for renin–angiotensin drugs as angiotensin-converting enzyme inhibitors
 - Primary healthcare center target rates for antibiotic prescribing
 - Percent of prescriptions for the penicillins versus other antibiotics

Economic interventions

- Devolved budgets to private primary healthcare centers with incentives for achieving budget goals and penalties for budget deficits
- Financial incentives for Catalan Health Service primary healthcare center physicians; target areas include:
 - General increase in the prescribing of generics
 - Incentives for increased prescribing of lower cost drugs, such as generic statins versus atorvastatin, generic proton pump inhibitors versus single-source proton pump inhibitors, generic antidepressants versus single-source antidepressants and generic angiotensin-converting enzyme inhibitors versus angiotensin receptor blockers
- Incentives can reach up to €6,000/physician (up to 15% of their annual salary). Prescribing indicator incentives account for approximately 27% of the overall indicators used for the physician financial incentive scheme
- Nonfinancial incentives are also offered to the minority of primary healthcare centers not managed by the Catalan Institute of Health

To date, there have been few published studies on the impact of the various national and regional initiatives on the utilization and expenditure of generic drugs, originators and single-sourced products in high-volume ambulatory-care prescribing areas in Spain [1]. One recently published study documented price reductions once multiple sources were available, averaging less than 30% in 2005 from the originator product prices for a basket of 12 products up to 3 years after first entry [6]. These included amoxicillin, lisinopril, metformin, omeprazole, paroxetine and simvastatin; we believe this is now an underestimate. In addition, further initiatives will still be needed in Catalonia to help ensure continued comprehensive and equitable healthcare.

Consequently, the aim of this study is to assess the impact of recent reforms and initiatives introduced nationally and in Catalonia on the utilization and expenditure of four high-volume classes in ambulatory care between 2003 and 2007 to provide guidance on future activities that could be undertaken in Catalonia to further enhance the quality and efficiency of ambulatory-care prescribing. This is in accordance with the recommendations of Antonñanzas and colleagues [1]. Future initiatives could be based on those successfully introduced in other European countries.

The four high-volume classes were the proton pump inhibitors (PPIs; Anatomical Therapeutic Chemical [ATC] Classification [110] – group A02BC), statins (C10AA) and ezetimibe (C10AX09), angiotensin-converting enzyme (ACE) inhibitors (C09AA and C09BA for single agents and combinations) and angiotensin

receptor blockers (ARBs; C09CA and C09DA for single agents and combinations), as well as the selective serotonin reuptake inhibitors (SSRIs) and newer antidepressants (venlafaxine, mirtazepine, reboxetine and duloxetine [N06AB and N06AX]) [110]. These four pharmacological groups were chosen because they are all high-volume prescribing and expenditure areas in ambulatory care, the products in the classes include single-source, originator and generic products and, with standards available as generics, they also include examples of product development (e.g., ARBs versus ACE inhibitors and isomers, such as escitalopram versus citalopram and omeprazole versus esomeprazole). These are typically more expensive once generics become available in a class and are heavily promoted by pharmaceutical companies.

We would expect increased prescribing of the statins in view of the prevalence of patients with lipid disorders in western Europe [111,112] and the acknowledged benefits of the statins in reducing cardiovascular events [10,11,111]. We would also expect increased utilization of ACE inhibitors, either alone or in combination, driven by the endorsement of their prescribing for hypertension, in patients with diabetes to help reduce renal complications, as well as cardiac insufficiency [106,113,114]. Finally, we also expect increased utilization of SSRIs and the newer antidepressants reflecting new indications such as social phobias and obsessive compulsive disorders, as well as increasing concerns with issues, such as dosing and compliance [115]. On the other hand, we would expect limited growth in the prescribing of PPIs with effective therapies to eradicate *Helicobacter pylori*, guidance

Table 2. Expenditure/defined daily dose (€) for originator and generic proton pump inhibitors from 2003 to 2007.

Drug	Type	Year			Reduction 2007 versus 2003 expenditure/defined daily dose (%)
		2003	2005	2007	
Omeprazole	Generic	0.50	0.27	0.19	62.4
	Originator	0.67	0.30	0.21	69.4
Pantoprazole	Generic			0.93	NA
	Originator	1.59	1.52	1.47	7.5
Lansoprazole	Generic*		0.96	0.89	11.9
	Originator	1.53	1.46	1.12	26.8
Rabeprazole		1.47	1.41	1.36	7.7
Esomeprazole			1.50	1.45	3.3 [†]

*Launched in 2004.
[†]Defined daily dose for esomeprazole has changed since 2003; consequently, only recent figures are included.
 NA: Not applicable.

advocating switching patients from healing to maintenance doses, as well as concerns with long-term consequences on increasing fracture and infection rates [12–16].

The analysis is from the payer's perspective. Catalonia was chosen for the analysis since it has above average rates for the percentage of generic prescriptions versus all prescriptions at 25.95% (in 2007) compared with the average of 20.94% across Spain. Rates were highest in Andalucía at 29.86% and lowest in Galicia at 9.79%. In addition, Catalonia is one of the principal autonomous communities in Spain active over a number of years, instigating a range of initiatives to try and influence prescribing (Box 1).

Materials & methods

Utilization of dispensed prescriptions among ambulatory-care patients, excluding hospital and over-the-counter prescriptions, covered by the National Health System in Catalonia was captured using DDDs, as well as DDDs per 1000 inhabitants per day (DDD/TID). Both these measures are internationally accepted to assess utilization [17,110,116], with the analysis of DDD/TID enabling comparison between countries with figures adjusted for the number of inhabitants in each country [17,116]. 2008 DDDs were used to enable comparisons to other published studies [110]. The DDDs used for the combination ACE inhibitors and ARB products were based on the DDD for the ACE inhibitor and ARB, respectively, if no dose was listed on the WHO website [110]. No ezetimibe and simvastatin combination was launched in Catalonia during the study period.

The analysis was confined to 2003–2007 as no comprehensive utilization and expenditure data were available before 2003. However, this time period did include the launch of a number of generics within the chosen classes, as well as the instigation of a number of reforms and initiatives. The population of the Catalan region ranged from 6.704 million in 2003 to 7.324 million in 2007 [117]. There was no adjustment for inflation during the study period.

The data for National Health Service patients in Catalonia was provided by the Catalonian Health Service DATAMART (dispensing register) database. The figures include originators, generics and single-source products in each class from the years 2003 to 2007. This is an internal database not open to the public (other regions will have different databases). Reimbursed expenditure has been used for the analysis to reflect the actual expenditure incurred by the Catalan Health Service. The reimbursed expenditure includes the ex-factory price together with wholesaler and pharmacist markup, and VAT at 4%. The wholesaler and pharmacist markups have changed marginally during recent years. During 2006–2008, markups were 7.6% for wholesalers and 27.8% for pharmacists [118].

Expenditures per DDD were computed for each product, including generics, to help assess the impact of the various initiatives on the prices of single-source, originator and generic products. Reimbursed costs and utilization in 2007 were also compared with 2003 to assess the impact of the various reforms and initiatives on overall utilization and expenditure of each product in each class, as well as help determine the key drivers of overall expenditure. However, no impact analysis was undertaken in view of the limited time frames available, coupled with the variable nature of the range and extent of the national and regional reforms and initiatives undertaken during the study period (Table 1 & Box 1).

An extensive literature review was undertaken in PubMed between 2000 and June 2009 using the keywords 'Spain', 'pharmaceuticals', 'reforms' and 'generics' to document the nature and content of national initiatives during this period. This was supplemented by the authors' knowledge of web references not included in the initial list of published papers coupled with knowledge of ongoing reforms in Catalonia to try and improve the quality and efficiency of prescribing.

There was no access to patient-specific data to assess, for instance, demographic changes during the study period, including any changes in the immigrant population, the medical rationale for the prescriptions, as well as any changes to doses prescribed, such as an increase in the dose of simvastatin following the heart protection study in patients with diabetes [10,11]. The change in the percentage of the population aged 65 years and older is especially important, since copayment stops once patients reach retirement age [102]. However, the percentage actually decreased from 17% in 2003 to 16.2% in 2007. Despite these limitations, we believe that the findings will be of interest to key stakeholders in Catalonia, as well as Spain in general, given the continued pressure on resources. The findings may also be of interest to health authority personnel in other European countries contemplating similar initiatives.

Results

Proton pump inhibitors

Proton pump inhibitor utilization grew steadily in Catalonia during the study period with the DDD/TID rising by 74% from 47.8 in 2003 to 82.8 in 2007. Omeprazole was the principal PPI prescribed at between 82 and 85% of total DDDs between 2003 and 2007, with limited prescribing of esomeprazole at only 4.3% of total PPI DDDs in 2007. Pantoprazole, lansoprazole and rabeprazole constituted the remaining DDDs. Generic omeprazole dominated omeprazole utilization at 84.9% of all DDDs dispensed in 2007, which was up from 66.3% in 2003.

Reimbursed expenditure/DDD for the PPIs as a class fell by just over 51% from €0.73 in 2003 to €0.36 in 2007, principally owing to the falling expenditure/DDD of omeprazole (TABLE 2). There was a more limited reduction in expenditure/DDD for esomeprazole, falling from €1.50 in 2005 to €1.45 in 2007. As a result of the decrease, the reimbursed expenditure for PPIs in Catalonia fell by €5.5 million from 2003 to €79.28 million in 2007. This equates to €10,825 per 1000 inhabitants per year in 2007, down from €12,796 per 1000 inhabitants per year in 2003.

Typically, there were greater reductions in expenditure/DDD of the various generics in 2007 compared with respective originator prices in 2003 than those presented in TABLE 2 when expenditures/DDD were just compared with pertinent generic costs in 2003 (see later section).

Statins & ezetimibe

Utilization of statins also grew steadily between 2003 and 2007, with the number of DDDs/TID at 92.97 by the end of 2007, an increase of 75.3% from 53.04 in 2003. Atorvastatin and simvastatin dominated statin utilization in Catalonia (FIGURE 1).

Generic simvastatin accounted for 81.6% of all simvastatin on a DDD basis in 2007, up from 35% in 2003. The expenditure/DDD for both originator and generic statins, especially simvastatin, decreased from 2003 to 2007 (TABLE 3). As a result, the reimbursed expenditure for statins was lower in 2007 (€103.8 million) compared with 2003 (€108.39 million) despite increased utilization (FIGURE 1). This equates to €14,174 per 1000 inhabitants per year in 2007, a decrease from €16,168 per 1000 inhabitants per year in 2003.

Reimbursed expenditure on ezetimibe was €7.63 million in 2007. This resulted in an increase in total reimbursed expenditure on the statins and ezetimibe versus statins alone by just over 7% to €111.44 million in 2007. As before, there were typically greater reductions in expenditure/DDD of the various generics in 2007 compared with respective originator prices in 2003 than those presented in TABLE 4, when expenditures/DDD were only compared with pertinent generic costs in 2003 (see later section).

Antidepressants

Only the SSRIs and newer second-line antidepressants were included in the analysis. Second-line antidepressants included venlafaxine, mirtazepine, reboxetine and duloxetine. Only these products were included owing to the following:

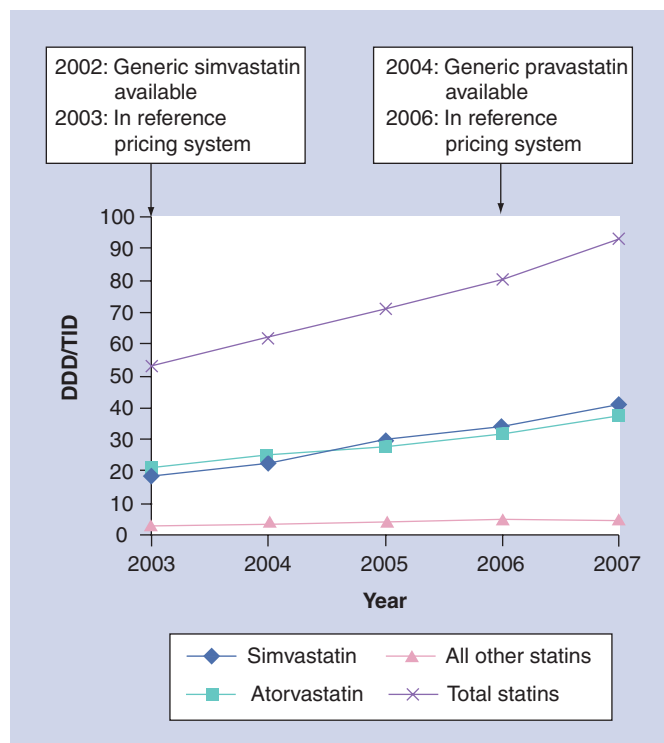


Figure 1. DDD/TID for statins in Catalonia 2003–2007. All other statins include fluvastatin, lovastatin and pravastatin. Rosuvastatin and cerivastatin were not available during the study years. DDD/TID: Defined daily dose per 1000 inhabitants per day.

- Until the 1980s, tricyclic antidepressants (TCAs) were the main drugs prescribed for depression. The TCAs were seen as effective but could have uncomfortable side effects impacting on compliance and effectiveness in practice [115,119];
- During the 1980s, the SSRIs were launched. The SSRIs were also seen as effective but with less side effects and improved tolerance versus the TCAs [119]. Improved tolerance led to improved compliance [18,19] and improved care versus the TCAs. As a result, the prescribing of antidepressants in ambulatory care during the 1990s and beyond heavily increased compared with the 1980s [119]. The other antidepressants, such as venlafaxine and mirtazepine, are typically used as second-line drugs [20–23].
- The SSRIs contain both originator, single-source and generic drugs, as well as isomers (escitalopram vs citalopram).

The utilization of the SSRIs, noradrenaline reuptake inhibitors and other dual-acting antidepressants (N06AB and N06AX) increased in Catalonia over the past 4 years with DDD/TID at 59.54 in 2007, an increase from 49.2 in 2003.

The SSRIs dominated utilization of the combined SSRIs and newer antidepressants at 80% of all utilization in 2007 on a DDD basis, a decrease from 85% in 2003. During this period, there was increased utilization of escitalopram and growth in the utilization of citalopram (FIGURE 2). Utilization of the remaining SSRIs marginally reduced during this period (FIGURE 2).

Table 3. Expenditure/defined daily dose (€) brand and generic statins from 2003 to 2007.

Drug	Type	Year			Reduction 2007 versus 2003 expenditure/defined daily dose (%)
		2003	2005	2007	
Simvastatin	Generic	0.64	0.28	0.17	74.3
	Originator	0.88	0.36	0.25	71.7
Pravastatin	Generic*		0.77	0.60	27.3
	Originator	1.14	1.10	0.79	30.1
Lovastatin	Generic	0.70	0.48	0.37	46.6
	Originator	0.77	0.52	0.39	48.5
Fluvastatin		0.67	0.62	0.59	12.5
Atorvastatin		0.80	0.69	0.60	25.2

*Launched in 2004.

Expenditure/DDD of both generic and originator SSRIs decreased during the study period, apart from escitalopram (TABLE 4). As before, there were typically greater reductions in expenditure/DDD of the various generics in 2007 compared with respective originator prices in 2003 than those presented in TABLE 4 when expenditures/DDD were only compared with pertinent generic costs in 2003. The prescribing of generic versus originator SSRIs increased for all four of the high-volume SSRIs during the study period (TABLE 5). There was lower utilization of generic mirtazepine and venlafaxine compared with originator drugs than seen with the SSRIs (TABLE 5). In the case of venlafaxine, only the immediate-release formulation was available as a generic during the study period, not the longer acting formulation, reducing generic utilization. Only the original and generic versions of mirtazepine were included in the homogenous class; the melt formulation was not included, again reducing the utilization of generic mirtazepine in practice (TABLE 5).

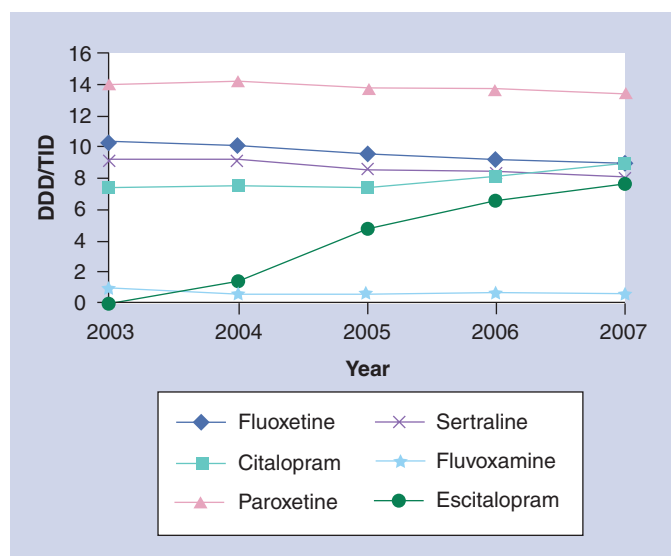


Figure 2. Utilization of selective serotonin reuptake inhibitors in Catalonia 2003–2007.
DDD/TID: Defined daily dose per 1000 inhabitants per day.

The fall in expenditure/DDD of the SSRIs coupled with increased prescribing of generic versus originator SSRIs resulted in the reimbursed expenditure of the SSRIs plus newer antidepressants falling from €121.29 million in 2003 to €118.34 million in 2007, despite increased utilization. This equates to €16158.0 per 1000 inhabitants per year in 2007 down from 18129.0 in 2003.

Renin–angiotensin drugs

The prescribing of renin–angiotensin drugs (ACE inhibitors and ARBs alone or in combination) increased by 29.9% from 117.7 DDD/TIDs in 2003, to 152.9 in 2007, driven by increased prescribing across all product categories (FIGURE 3).

Expenditure/DDD of originator and generic ACE inhibitors alone or combination decreased in 2007 compared with 2003 (TABLE 6). This resulted in the overall expenditure/DDD for ACE inhibitors falling from €0.27 in 2003 to €0.13 in 2007. Overall expenditure/DDD of the ARBs alone or in combination also fell marginally during this period from €0.68 in 2003 to €0.60 in 2007 following the availability of generic losartan in 2006.

These reductions in expenditure/DDD of the various products helped to moderate the rise in reimbursed expenditure for the combined renin–angiotensin drugs to 11.5% in 2007 versus 2003, despite an approximate 30% increase in utilization. The combined expenditure on the various renin–angiotensin products was €129.51 million in 2007. This equates to €17,683 per 1000 inhabitants per year in 2007, a marginal increase from €17,329 per 1000 inhabitants per year in 2003.

As before, there were typically greater reductions in expenditure/DDD of the various generics in 2007 compared with pertinent originator prices in 2003 than those presented in TABLE 6, when expenditures/DDD were just compared with relevant generic costs in 2003 (see later sections).

Expert commentary & five-year view

General

Analysis of ambulatory-care expenditure and utilization of the various drugs in the four high-volume prescribing areas showed a substantial reduction in expenditure/DDD of generics and originator products in 2007 versus 2003, demonstrating the positive impact of recent initiatives. This is in line with expectations based on the range of measures introduced nationally and regionally over the study period (TABLE 1 & BOX 1), and significantly greater than the reductions of less than 30% for 12 products seen up to 3 years after the first generic entry documented in a recent publication [6]. For instance, expenditure/DDD of generic and originator simvastatin was 81.2 and 71.7%, respectively, below 2003 originator prices (i.e., just 20–30% of originator 2003 prices). The expenditure/DDDs achieved for generic omeprazole and generic simvastatin, for instance, provides an example to a

Table 4. Expenditure/defined daily dose (€) brand and generic serotonin reuptake inhibitors.

Drug	Type	Year			Reduction 2007 versus 2003 expenditure/defined daily dose (%)
		2003	2005	2007	
Fluoxetine	Generic	0.63	0.36	0.22	65.2
	Brand	0.77	0.59	0.44	43.2
Citalopram	Generic	0.78	0.66	0.41	47.0
	Brand	0.94	0.74	0.55	41.5
Paroxetine	Generic	0.86	0.75	0.70	37.4
	Brand	1.11	0.99	0.75	32.3
Sertraline	Generic		0.58	0.35	61.2
	Brand	0.89	0.85	0.61	32.2
Escitalopram			0.85	0.83	3.4*

*2007 versus 2005.

number of other European countries seeking to release further resources from generic availability. Expenditure/DDD for generic omeprazole at €0.19 is similar to England [NLT PCT, UNPUBLISHED DATA] and marginally lower than Sweden [2] but, for instance, two- and three-times lower than Austria and Germany, respectively [9,24]. The expenditure/DDD of generic simvastatin at €0.17 is appreciably more expensive than prices seen in England [NLT PCT, UNPUBLISHED DATA] or Sweden [2], but lower than Austria (€0.29) and Germany (€0.20) [9,24]. Consequently, there may be an opportunity for further savings in statin expenditure with the potential for lower prices for generic simvastatin. Alongside this, the various measures have also resulted in increased utilization of generic versus originator drugs, further endorsing their positive impact. The utilization of generics may well rise further with potential reluctance of originator manufacturers to continue to lower their prices to retain at least some market share coupled with continued educational and other initiatives endorsing the prescribing of generics within a class. The increased utilization of generics versus originators, coupled with lower expenditure/DDD for the various classes as a whole, led to reimbursed expenditure for a number of the classes actually falling during the study period despite increased utilization, again demonstrating the positive impact of the various reforms. We accept that there are limitations with the study design. These include the fact that it is difficult to state whether we have fully captured all the relevant demand side initiatives and reforms (Box 1). In addition, a number of generic ACE inhibitors, PPIs and statins were launched and included in the reference price system before 2003. In addition, the number and extent of supply-and-demand side initiatives introduced nationally, as well as variably across the region during the study period (Table 1 & Box 1), made it difficult to undertake an impact analysis when combined with the limited number of time points. Consequently, none were undertaken. Finally, we do not know whether there have been any major changes in prescription doses for the classes over time owing to educational activities or any major demographic changes or case mix changes that

may influence prescribing. This is because we did not have access to patient-specific data. As stated, however, the percentage of patients aged 65 years or greater marginally fell during the study period. However, we believe that some conclusions can be drawn from the findings to guide future activities in Catalonia (Table 1 & Box 1). We also believe there are potential learnings from Catalonia that may be of interest to other regions in Spain and beyond, as well as possible initiatives that could be introduced in the future in Catalonia to further enhance the efficiency of prescribing. These support ongoing initiatives in other European countries.

Reforms impacting on prices

As demonstrated, the recent initiatives have resulted in continuing falls in expenditure/DDD for the generics in each of the major classes despite a number of generic formulations being launched and included in the reference pricing system before the start of the study period. When comparing 2007 expenditure/DDD of various generics with pertinent 2003 originator prices, these include the following:

- PPIs: 72.2, 41.4 and 41.3% reduction for generic omeprazole, lansoprazole and pantoprazole, respectively;
- Statins: 81.2, 51.2 and 47.1% reduction for generic simvastatin, lovastatin and pravastatin, respectively;
- SSRIs: 65.2, 47.4 and 47.4% reduction for generic fluoxetine, citalopram and sertraline, respectively;
- ACE inhibitors: 61.5, 47.8, 38.0 and 47.8% reduction for generic enalapril, ramipril and lisinopril, respectively.

Table 5. Extent of prescribing of generic antidepressants versus originator products 2003–2007.

Antidepressant	Year		
	2003	2005	2007
Generic fluoxetine versus total fluoxetine (%)	44.4	56.4	66.1
Generic citalopram versus total citalopram (%)	5.1	36.7	61.7
Generic paroxetine versus total paroxetine (%)	13.3	40.4	52.9
Generic sertraline versus total sertraline (%)		17.5	35.0
Generic mirtazepine versus total mirtazepine (%)		5.2	16.9
Generic venlafaxine versus total venlafaxine (%)		0.1	2.6

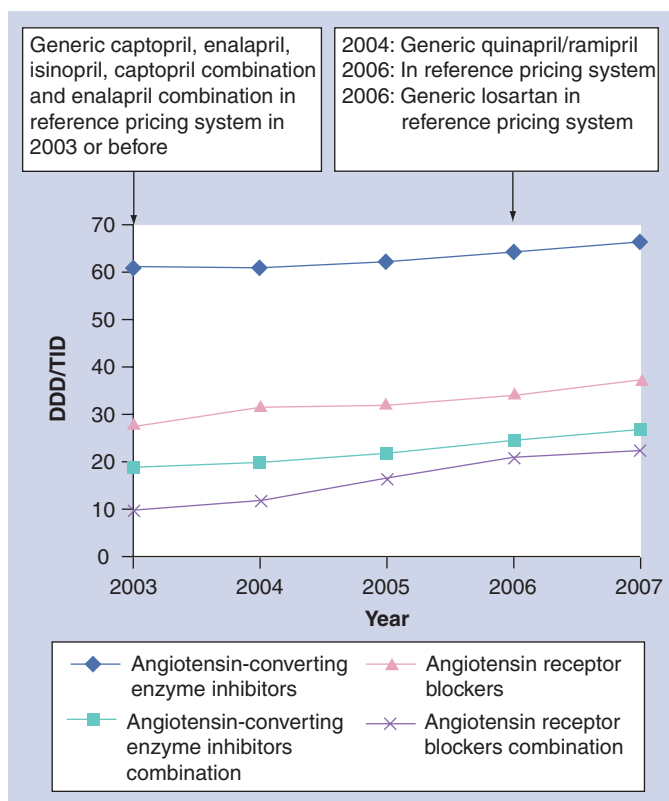


Figure 3. Total utilization of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers 2003–2007 (DDD/TID). Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers refer to single products not combined with a diuretic or other antihypertensive drugs in the same tablet. DDD/TID: Defined daily dose per 1000 inhabitants per day.

In addition, it is highly likely that the reduction in the expenditure/DDD for a number of generics would have been greater if we were able to compare 2007 expenditure/DDD with originator prices prepatent loss and not just from 2003 (i.e., before a number of generic formulations were launched and included in the reference pricing system). This would further demonstrate the successful impact of widening the 2003 reference pricing initiative endorsing its continuation [1].

As discussed, the substantial reductions in generic expenditure/DDD seen in practice in Spain, especially for generic omeprazole and generic simvastatin, also serve as good examples to other European countries with much higher expenditures/DDD [25,26].

We also note that there are differences in the rate of reduction in expenditure/DDD for the various generics in 2007 versus originator prices in 2003, both within and between classes. However, analysis of the underlying rationale for this are outside the scope of this article as this may be due to a number of factors we have not analyzed. A similar picture is also seen in other European countries [2,9]. Potential reasons could include, for instance, differences in the complexity of manufacture, originator firms successfully defending their patents, as well as possible differences in commercial pressures among generic companies to have their products preferentially dispensed in community pharmacies.

Not surprisingly, in view of the reforms (TABLE 1), there have also been corresponding falls in expenditure/DDD of the originator products and, to a lesser extent, single-source products in the class to compete once generics are launched (TABLES 2–4 & 6). However, expenditure/DDDs for originator products were generally higher than those for the corresponding generics, although less so for the ACE inhibitors. This limited their utilization in practice, ranging, for instance, from 15 to 20% of total DDDs for the molecule for originator lansoprazole, omeprazole and simvastatin. However, utilization of originator SSRIs was higher, ranging from 34 to 65% of total utilization for the products in 2007 (TABLE 5). This may, in part, reflect differences in doses prescribed between the formulations. In addition, manufacturers of the originators may be more willing to price their products below the current reference price to enhance their dispensing. Alternatively, they may instigate other measures with community pharmacists to enhance their market share. However, these are speculations as further analysis is difficult without access to specific patient and pharmacy data.

As discussed earlier, the situation is different for venlafaxine and mirtazepine, where only the original formulations were available and included in the reference price system during the study period and not the extended-release or melt formulations, respectively. This is likely to change once both products are included in the reference price system.

Reforms impacting on prescriptions & volumes

There appears to be a more mixed impact on the various demand-side initiatives (Box 1) on the influence of prescribing generics first line instead of single-sourced products. This may reflect the fact that it is harder to influence prescribing decisions, both in terms of products prescribed and their volume, than it is to directly influence drug prices [8]. This is because regulations to influence prices, substitution and the extent of any copayment for more expensive brands are typically instigated through, for example, new laws. Initiatives to influence prescribing generally involve multiple interventions to be successful [2], including education, peer pressure and financial incentives. However, none of these so-called 'soft regulations' are truly enforceable, and rely on peer pressure and other factors, such as financial incentives, for success [8].

However, the prescribing rates for the various generics in the classes versus originators were substantially higher than previously documented rates of only 10–25% for 12 products up to 3 years after generic availability in a recent publication [6]. This, again, demonstrates the successful impact of recent national and regional initiatives in Spain.

Proton pump inhibitors

As seen, there is a high rate of prescribing of generic omeprazole compared with the originator, as well as with other PPIs, including other generic and single-sourced PPIs. This, combined with falling expenditure/DDD for both the generics and originator brands, helped to decrease reimbursed expenditure in 2007 versus 2003, despite significantly increased volumes. We believe it is highly likely that this prescribing pattern was helped by the range of educational and engineering activities instigated in Catalonia, serving as an

example to other regions in Spain and other countries. However, we cannot say this with certainty, as we were unable to undertake any impact analysis.

However, a surprising finding was the growth in utilization of the PPIs over the study period matching the growth rate seen for the statins, especially as there are effective therapies to eradicate *H. pylori*, guidelines encouraging dropping the doses prescribed to a maintenance dose, and concerns with chronic prescribing on increasing fracture and infection rates. The rate of increase of PPI utilization, at 74% between 2003 and 2007, however, was lower than that seen in Germany during this period [24] and lower than the threefold increase seen in some European countries between 2001 and 2007 [9,25].

This increase may reflect growing prescribing for uncomplicated dyspepsia, especially as recent reviews have shown that there appears to be no approved indication for between 25 and 70% of all PPI prescriptions [27], and PPIs can be successfully discontinued in 27% of chronic users [28]. One way forward could be to introduce further financial and other incentives to reduce the prescribing for nonspecific dyspepsia, which is already starting to happen in Catalonia. Similar initiatives have also been introduced in other countries, including Stockholm County Council in Sweden [2]. Following implementation, we would expect moderation in the prescription growth helping to keep expenditure under control. If this is seen in practice, Catalonia can serve as another example to other regions in Spain and countries where there are high and growing rates of PPI prescribing.

Statins & ezetimibe

The increase in the utilization of statins reflects findings from across Europe [9,17,24,26] in view of the prevalence of patients with lipid disorders in western Europe [111,112], and the acknowledged benefits of the statins in reducing cardiovascular events [10,11,111].

We believe the educational and engineering activities instigated in Catalonia during the study period helped counterbalance the impact of commercial activities to increase the prescribing of atorvastatin versus generic simvastatin, as a result, helping to lower statin expenditure over time despite increased utilization. However, again, it is difficult to state this with absolute certainty. Next steps could include greater financial incentives to proactively enhance therapeutic substitution through actively switching patients from, for instance, atorvastatin 10 mg to generic simvastatin 20 mg. This builds on current schemes in Catalonia matching initiatives in other European countries, where therapeutic substitution has been implemented successfully [29,30]. If this fails to significantly reduce prescribing of atorvastatin, then, with

Table 6. Expenditure/defined daily dose (€) for selected originator and generic angiotensin-converting enzyme inhibitors 2003–2007 based on their prescribed volumes.

Drug	Type	Year			Reduction 2007 versus 2003 cost/defined daily dose (%)
		2003	2005	2007	
Enalapril	Generic	0.21	0.11	0.09	57.0
	Originator	0.23	0.13	0.10	57.0
Lisinopril	Generic	0.26	0.19	0.17	35.4
	Originator	0.27	0.24	0.18	32.3
Ramipril	Generic		0.24	0.18	31.3
	Originator	0.34	0.30	0.21	37.1
Captopril + diuretic	Generic	0.42	0.38	0.34	19.8
	Originator	0.48	0.42	0.34	28.7
Enalapril + diuretic	Generic	0.20	0.18	0.12	37.0
	Originator	0.27	0.20	0.15	45.2
Losartan	Generic			0.58	-1.0*
	Originator	0.91	0.87	0.63	30.8
Eprosartan	Originator	0.90	0.87	0.83	7.9
Valsartan	Originator	0.71	0.68	0.65	8.7
Candesartan	Originator	0.53	0.51	0.44	16.2

*Launched in 2006.

the assistance of other autonomous communities, representation could be made to the national reimbursement agency to restrict the reimbursement of atorvastatin to second line for patients failing to attain target lipid levels on generic statins. These initiatives have already successfully been introduced in other European countries (e.g., Austria, Norway and Sweden) [9,31,112]. In Austria, for instance, total DDDs for atorvastatin fell to just over 10% of all statin DDDs 3 years after ambulatory-care physicians were required to seek the permission of the Chief Medical Officer of the patient's social health insurance company for atorvastatin to be reimbursed [9].

Sales of ezetimibe in Catalonia were €7.63 million at the end of 2007 (6.9% of all reimbursed expenditure on statins and ezetimibe). This is, despite doubt, regarding the actual level of benefits in reality [24,32,33]. Consequently, this is another potential area for educational activities and incentive schemes until more data are available about the long-term benefits of ezetimibe.

Antidepressants

The increased utilization of SSRIs coupled with the newer antidepressants is in line with expectations. It is, perhaps, not surprising that SSRIs dominated the prescribing of this selected group of antidepressants as SSRIs are routinely recommended first line for depression in national and local prescribing guidelines [2,119]. Drugs such as venlafaxine and mirtazapine, with their dual activity, are typically relegated to second-line use with published studies, showing increased efficacy over SSRIs [20–23].

However, there are concerns with the growing prescribing of escitalopram versus other SSRIs, including citalopram [120,121], although recent reviews have shown some benefit for escitalopram versus citalopram [34]. This has typically led to citalopram rather than escitalopram being advocated as part of first-line treatment for depression (e.g., by Stockholm County Council in Sweden) [2]. As a result, there is an opportunity for savings if new patients are started on a generic SSRI rather than escitalopram, with current expenditure/DDD of escitalopram substantially greater at €0.83 in 2007 than generic citalopram, fluoxetine or sertraline (TABLE 4).

There is also the opportunity for considerable savings with encouraging greater prescribing of generic mirtazepine rather than the melt formulation. This is the situation in Austria where generic mirtazepine is utilized in nearly all cases [GODMAN B. UNPUBLISHED DATA]. Potential ways to encourage this could be through incentive schemes for the generic product group linked with specific prescribing targets, as seen in Stockholm County Council in Sweden. In 2007, the target was more than 90% for generic mirtazepine versus all mirtazepine on a DDD basis, including the melt formulation [2].

Finally, there is also an opportunity for future savings through the increased prescribing of generic venlafaxine versus originator extended-release venlafaxine in suitable patients (TABLE 5). Expenditure should start to fall once generic extended-release venlafaxine, which has been launched recently, is included in future reference price schemes.

ACE inhibitors/ARBs

Increased utilization of renin–angiotensin products is, again, in line with expectations. However, there are concerns with the growing prescribing of ARBs alone or in combination with significant differences in expenditure/DDD once generic ACE inhibitors became available (TABLE 6) and no apparent difference in effectiveness between the various antihypertensive agents, apart from, perhaps, β -blockers in the elderly [122]. ARBs are still required in a small minority of patients experiencing coughing serious enough to impact on compliance necessitating a switch [35,123]. Consequently, there is an opportunity to conserve costs in the future without compromising care through encouraging increased prescribing of generic ACE inhibitors first line. Potential measures to achieve this could, again, include greater financial incentives for prescribing ACE inhibitors first line, building on prescribing targets in, for instance, Sweden and the UK [2,124]. This could be combined with possible patient surveys to assess current indications for the prescribing of ARBs [36] as a prelude to instigating additional educational activities with relevant physicians if needed. In addition, therapeutic ARB substitution, now that generic ARBs are available, should be

encouraged. Therapeutic substitution of ARBs has been carried out successfully in other European countries [29,30]. The resources released used to enhance compliance, which is always a concern for chronic asymptomatic conditions, such as hypertension [37,113].

If still needed, possible progression could again include putting pressure on the national reimbursement agency to restrict prescribing restrictions on ARBs (i.e., they can only be prescribed after patients are experiencing side-effect problems with ACE inhibitors). This is the current situation in Sweden [122], with early analysis showing that such restrictions are working with a reduction in the number of patients prescribed an ARB without first being prescribed an ACE inhibitor [38].

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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Anna Coma and Corrine Zara are employed by the Catalan Health Service, and Antonia Agustí and Eduardo Diogène provide services to the Catalan Institute of Health. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Key issues

- Recent national and regional reforms and initiatives in Spain have been successful in reducing expenditure/defined daily dose (DDD) of both generics and originators in line with expectations (e.g., an 81.2% reduction in expenditure/DDD of generic simvastatin and 72.2% for generic omeprazole in 2007 versus 2003 originator prices). The reductions in expenditure/DDD have been substantially greater than previously published declines, leading to overall falls in reimbursed expenditure for the proton pump inhibitors, statins and selected antidepressants over the study period, despite increased utilization.
- The utilization of generics in the four classes versus originator products has also been appreciably higher than previous publications, further demonstrating the success of recent measures.
- The substantial utilization of generic omeprazole versus other proton pump inhibitors reflects the successful impact of recent initiatives in Catalonia. Recent initiatives to encourage the prescribing of generic simvastatin versus atorvastatin and generic angiotensin-converting enzyme inhibitors versus angiotensin receptor blockers have been less successful, although it is likely that the prescribing of these products would have been greater without the counterbalancing initiatives of the Catalan Health Institute. These are targets for future campaigns, building on existing measures helped by the availability of generic angiotensin receptor blockers.
- Further reforms and initiatives will be needed to keep ambulatory-care expenditure under control in Catalonia. There are opportunities for Catalonia to learn from other European countries, such as restricted reimbursement schemes; however, these have to be applied nationally through combined pressures from the autonomous communities.

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