Impact of drug safety warnings and cost-sharing policies on osteoporosis drug utilization in Spain: intense reduction with over and underuse persistence

Isabel Hurtado-Navarro, Aníbal García-Sempere, Clara Rodríguez-Bernal, José Sanfélix-Genovés, Salvador Peiró, Gabriel Sanfélix-Gimeno

Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunidad Valenciana (FISABIO)
Red de Investigación en Servicios de Salud en Enfermedades Crónicas (REDISSEC)
Pharmacological secondary prevention after hip fracture—with bisphosphonates or alternative drugs—is recommended by virtually all clinical practice guidelines (CPG).

Pharmacological primary prevention is controversial and CPGs are extraordinarily variable in the assessment of fracture risk factors, risk thresholds, drug risk assessment and recommendations of pharmacological treatment in previously non-fractured patients.

Spain is one of the European (and worldwide) countries with a lower incidence of osteoporotic fracture but osteoporosis drug consumption experienced a very rapid growth during the 2000s, being one of the countries with the highest utilization rates at the end of that decade.

The prevalence of osteoporosis drug treatment in 2010 was about 28% in women aged 50 and over.

About half of osteoporosis treatment in Spain have been evaluated as unnecessary according to Spanish or international CPGs.
Studies in several countries show a significant decrease in the consumption of osteoporosis drugs from a peak around 2009. This fall has been mainly attributed to safety warnings issued by regulatory agencies on jaw osteonecrosis, atypical fractures and esophageal cancer, and also to uncertainty about optimal bisphosphonate treatment duration and recommendations of discontinuation after 3 to 5 years of therapy.

---

**Nov 8, 2005**

Bisfosfonatos de administración parenteral y osteonecrosis del maxilar.

**Set, 2009**

*Recomendaciones para la prevención de la osteonecrosis del maxilar asociada al tratamiento con bisfosfonatos*

**Apr, 2011**

*Bisfosfonatos y riesgo de fracturas atípicas de fémur*

**Mar, 2012**

Ranelato de estroncio (osseor®, protelos®): riesgo de tromboembolismo venoso y reacciones dermatológicas graves. Nuevas contraindicaciones de uso

**Jul, 2012**

Calcitonina: uso restringido a tratamientos de corta duración

**Apr, 2013**

Calcitonina: suspensión de la comercialización de los preparados intranasales y restricción del uso de los preparados inyectables a tratamientos de corta duración

**Apr, 2013**

Ranelato de estroncio (osseor®, protelos®): riesgo de infarto agudo de miocardio

**Jan, 2014**

Ranelato de estroncio (osseor®, protelos®): la revisión europea concluye que el balance beneficio-riesgo es desfavorable

**Feb, 2014**

Finalización de la revisión del balance beneficio-riesgo de ranelato de estroncio (osseor®, protelos®): restricciones de uso

**Jul, 2014**

Ranelato de estroncio (osseor®, protelos®): calificado como medicamento de diagnóstico hospitalario

**Set, 2014**

Denosumab (Prolia®, Xgeva®): riesgo de osteonecrosis mandibular e hipocalcemia
The safety warnings on bisphosphonates (the most prescribed osteoporosis drug class) issued by the Spanish Agency for Drugs and Medical Products (AEMPS) and the modification of the cost-sharing scheme may have produced a reduction in the global prescription of osteoporosis drugs.

As drug agencies maintained in their warnings a positive risk-benefit balance in high-risk patients, this reduction may occur mainly in people with a low risk of fracture (young people, without risk factors for secondary osteoporosis, without previous fracture or with low-risk scores in the Fracture Risk Assessment Tool (FRAX®)), reducing overuse but keeping –or at least reducing to a lesser extent– appropriate prescription in high-risk patients.
To assess changes in the utilization of osteoporosis drugs in the Valencia Region (Spain) after the issue of safety warnings from regulatory agencies and cost-sharing changes, according to socio-demographic and risk of fracture patient characteristics, using 2009-2015 data from the ESOSVAL prospective cohort.
We use 2009-2015 data from the ESOSVAL prospective cohort to describe changes in osteoporosis drug consumption according to sociodemographic and clinical risk factors at baseline.

The ESOSVAL cohort was composed of about 11,000 people aged 50 years and over attending 272 primary healthcare centers in the Valencia Health System (VHS) for any health problem between November 2009 and September 2010.

Participants were recruited by 600 general practitioners and primary-care nurses collaborating for free in the ESOSVAL study and following predefined criteria attempting to obtain a similar number of men and women, and with an age distribution as close as possible to the distribution of the region’s population.
ESOSVAL cohort (n=11,035; women: 48%; men: 52%; mean age: 65 years old) who attended primary care consultations for reasons unrelated to osteoporosis.

Exclusion criteria: temporary residents, cognitive impairment, people receiving their usual care through private insurance companies, physically unable to attend their primary healthcare center, and people of Asian or African descent.
**Persons and Methods**

- We estimate the **monthly proportion of patients treated with any osteoporosis drug (except zoledronic acid)** according to sociodemographic and risk variables at baseline, and we **calculate the risk ratio (RR) of being treated each month with respect to the first month** of the corresponding series (January 2009). People who died were excluded from the denominator in the month of death.

- We used **interrupted time series** and **segmented linear regression models** to assess changes in osteoporosis drug utilization while controlling for previous levels and trends after three natural intervention dates: the **AEMPS osteonecrosis jaw warning publication** (Sept 2009), the **AEMPS atypical femur fracture warning publication** (Apr 2011) and the **modification of the cost-sharing scheme on pharmaceuticals** (Jul 2012).

- Trends are presented in **natural scale** (proportion of people treated) and in **RR scale** (ratio between the proportion of people treated each month and the proportion of people treated in January 2009) to compare the relative variations between strata in homogeneous terms.
**Results**

- **From 10.6% in Jan 2009** to a peak of 13.5% in May 2010, descending from that month to **6.7% in Dec 2015**, a relative reduction of 59% from Jan 2009, and of 104% from the peak of treatment.

- Trends were rising until the atypical fracture warning issue in Apr 2011, starting a downward trend until the end of the period, only altered by a sudden jump down associated with the cost-sharing policy change in Jul 2012.

- Similar trends in people 50-64y and 65 and over
Results

Similar patterns in women and men, but men show a higher initial relative growth.
Results

Osteoporosis treatment segmented linear regression trends 2009-2015 stratified by Frax 10y Hip Risk Fracture

Osteoporosis treatment segmented linear regression trends 2009-2015 stratified by previous fracture
Results

Figure S11. Annual consumption of antosteoporosis drugs 2009-2015

Figure S12. Market Share of osteoporosis drugs 2009-2015.
Discussion

Osteoporosis drug utilization increased until mid-2011 and then started to decline so that by the end of 2015 global consumption was around a half of 2009 and almost two thirds less than the maximum peak in 2010.

The safety warning on bisphosphonates (Apr2011) and to a lesser extent the increase in the pharmaceutical copayment (with a sudden descent in the months immediately after Jul2012 but without altering the temporary trend) seem to have a strong influence on this decline.

Decline does not seem to be related with the clinical characteristics of patients, as we observe a relative similar decline in those with a high and a low risk of fracture.

To the best of our knowledge, no previous studies in this field have assessed the impact of warnings on several risk strata (age, gender, risk of fracture).
Discussion

The decrease in the consumption of osteoporosis drugs happened at an earlier moment in other countries with a maximum peak in 2009 and starting to fall in 2010 coinciding with the FDA warning on the association between bisphosphonates long-term use and atypical fractures. The Spanish Agency for Medicines and Medical Devices did not publish the warning on atypical fractures (simultaneously with the European Medicines Agency) until mid-2011, a year after the FDA warning.

Other factors may have contributed to the decline in the consumption of osteoporosis drugs in Spain: the expiration of most patents, with the associated cessation of pharmaceutical promotion and proprietary firm efforts to neutralize the impact of warnings, the contagion from safety warnings on other osteoporosis drugs,
Limitations

- We use baseline characteristic of the ESOSVAL cohort to stratify the risk of fracture,
- we have no information on zoledronic acid consumption,
- we have not analyzed the importance of the possible mechanisms operating in the decrease of osteoporosis drug consumption (non-adherence, discontinuation, therapeutic holidays, decrease of initiators or others)
- Doctors who enrolled patients in the ESOSVAL cohort were object of an educational intervention coinciding with the cohort recruitment period (2009-2010), an aspect that could have modified the initial prescription behavior
Conclusions

- The AEMPS osteonecrosis jaw warning of Sept 2009 was not associated with a decline in the consumption of osteoporosis drugs, while
- the AEMPS atypical fracture warning of Apr 2010 was associated with a significant decrease in the number of people treated, reinforced by the increase in the pharmaceutical copayment in 2012.
- As a result, in December 2015 only half of the patients of May 2010 (the month with the highest proportion of treatment) were in treatment.
- Decreases in treatment affected both patients at a low risk of fracture and those at a higher risk.
Thanks
Funding and competing interests

The ESOSVAL research program is co-funded by the Instituto de Salud Carlos III (Grants PS09/02500, PI11/00238 and PI13/01721) from the Spanish Ministry of Health and the European Regional Development Fund, and by collaboration agreements established by FISABIO and the Valencia Department of Health with MSD Spain (2009–2012) and AMGEN S.A. (2010–2013), to conduct training and real-world research into musculoskeletal disorders and osteoporosis.

From 2013 our research group is part of the Red de Investigación en Servicios de Salud en Enfermedades Crónicas (REDISSEC), co-funded by the Instituto de Salud Carlos III (Grants PS09/02500, PI11/00238 and PI13/01721) from the Spanish Ministry of Health and the European Regional Development Fund.

None of the sponsors played any role in the design of the ESOSVAL studies, the collection, analysis or interpretation of data, the writing of manuscripts or in the decisions to submit research works for publication.