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**Changes in the Utilization of Osteoporosis Drugs after the 2010 FDA
Bisphosphonate Drug Safety Communication**

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Changes in the Utilization of Osteoporosis Drugs after the 2010 FDA Bisphosphonate Drug Safety Communication

Abstract

INTRODUCTION: In October 2010, the US Food and Drug Administration (FDA) issued a safety communication regarding the risks of atypical fractures of the femur, with bisphosphonates drugs. This study evaluated the impact of the bisphosphonates FDA safety communication on the utilization of osteoporosis medications in Medicaid programs.

METHODS: Osteoporosis drugs utilization data from the July 2006 to June 2014 were extracted from the national Summary Files from the Medicaid State Drug Utilization Data maintained by the Centers for Medicare & Medicaid Services (CMS). We performed an interrupted time series analyses to evaluate trends in utilization of osteoporosis drugs before and after the 2010 FDA safety communication.

RESULTS: Time-series analyses of osteoporosis drug utilization in Medicaid program revealed a significant downward trend associated with the 2010 FDA bisphosphonates safety communication. Before the FDA safety communication was issued, the utilization rate was slightly decreased between 2006 and 2010. In the year following the FDA safety communication the bisphosphonate DDDs per 1000 beneficiaries of fell 22% yearly until the end of study period.

CONCLUSIONS: The 2010 FDA bisphosphonates safety communication appeared to have influenced Osteoporosis utilization in Medicaid recipients. The 2010 FDA bisphosphonates safety communication was associated with a significant reduction in the utilization of bisphosphonates in the Medicaid program.

KEY WORDS: Medicaid; osteoporosis; bisphosphonate; US Food and Drug Administration; regulatory warning; Utilization.

ACCEPTED MANUSCRIPT

Introduction

Bisphosphonates are currently considered the first-line therapy for the prevention and treatment of osteoporosis. In the United States (US), 14.7 million prescriptions of oral bisphosphonates were dispensed in 2012.¹ Alendronate was the first bisphosphonate to obtain FDA approval for the treatment and prevention of osteoporosis, followed by the approval of several bisphosphonates with different efficacies and dosing regimens.^{2,3}

Several studies indicated the association between the long-term use of bisphosphonates and the risk of atypical fracture of the femur.⁴⁻⁶ The FDA reviewed these data and issued a Drug Safety Communication (DSC) in 2010 regarding the risk of atypical femur fractures associated with the long-term use of bisphosphonates. The FDA required drug manufacturers to include a limitation of use statement, “The optimal duration of use has not been determined. For patients at low-risk for fracture, consider drug discontinuation after 3 to 5 years of use,” on the label of all bisphosphonates approved for the treatment of osteoporosis.⁷ In addition, a medication guide should be given to the patient with each bisphosphonate prescription describing the risk and symptoms of these fractures.⁷ The labeling changes and medication guide affected several brands of bisphosphonates approved for osteoporosis and their generic products (e.g., alendronate, alendronate and cholecalciferol, risedronate, risedronate delayed release, ibandronate, zoledronic acid).⁷

Despite the high prevalence and economic burden of osteoporosis, the literature on the utilization and spending on osteoporosis drugs is scarce.^{8,9} Furthermore, no empirical studies have been conducted assessing trends in the utilization and spending on osteoporosis drugs and the changes in the patterns of bisphosphonate utilization in the

Medicaid program following the DSC are unknown. In an attempt to understand how the FDA safety recommendation actions affected prescribing practices, we investigated the utilization of bisphosphonates before and after FDA regulatory actions in the Medicaid program from July 2006 through June 2014.

Material and Methods

Data Sources

The primary data source is the National Summary Files from the Medicaid State Drug Utilization Data maintained by the Centers for Medicare and Medicaid Services (CMS). The data are fee-for-service pharmacy claim records for outpatient drugs dispensed. This data set is available for 49 states (except Arizona) and the District of Columbia; it includes only outpatient pharmacy prescriptions reimbursed by Medicaid in the period July 2006 through June 2014.¹⁰

Each data record of this dataset includes: drug name, national drug code (NDC), units reimbursed, number of prescriptions, and total pharmacy reimbursement amount including drug cost and dispensing fees. An updated list of osteoporosis drugs marketed in the US was obtained from the U.S. Food and Drug Administration (FDA) online databases. All osteoporosis drugs were identified by their national drug codes (NDCs) using the FDA NDC directory.¹¹ Information on missing NDCs in the FDA NDC directory was compiled from Physicians' Desk Reference (PDR).

The FDA regulatory data and the Medicaid state drug utilization data for each osteoporosis drug were merged to create a unique dataset that contained FDA regulatory data and Medicaid utilization using the NDC and drug name.

Data Analysis

Drug utilization was measured by the total defined daily doses (DDD). All drug units (e.g., tablets, nasal spray, injections) were converted to DDDs using the World Health Organization Anatomical Therapeutic Chemical/Defined Daily Dose (WHO ATC/DDD) index.¹² When the DDD was not available, the daily dose was calculated using the FDA labeling information for drugs which is available on the FDA website. This method allows for a comparison of the utilization and spending of different osteoporosis drug classes using a standardized unit.

We conducted an interrupted time series analysis (ITS) to assess the association of the 2010 FDA DSC on the utilization of bisphosphonates in the Medicaid program.¹³⁻¹⁵ Interrupted time design is one of the strongest quasi-experimental designs to assess the longitudinal effects of an intervention.^{16,17}

Autoregressive integrated moving average (ARIMA) techniques are well established in the literature to perform a time series analysis.¹⁸⁻²² In contrast with other techniques like a simple pre- and post-intervention means test which results in overestimation or underestimation of effect, ARIMA modeling takes into account secular trends and it only requires data of the variables of interest for the analysis. Additionally ARIMA is more flexible than other techniques in fitting the data.²²⁻²⁴

Osteoporosis drug utilization and pharmacy reimbursement were calculated per 1,000 Medicaid beneficiaries to account for changes over time in the number of Medicaid beneficiaries. The time series ARIMA model also controlled for the demographic changes in the Medicaid population adjusting for the proportion of women 65 years and over.

A stepwise approach was used to select the best fit model by adding different parameters to the model such as availability of competitors' drugs, introduction of new drugs and generic entry.. Akaike Information Criteria (AIC) were used to select the best fitting model. Statistical significance was set at 0.05 (two-sided). All statistical analyses were performed using SAS software, version 9.4 for Windows (SAS Institute, Inc., Cary, NC, USA).

Results

Five drug classes were used in this study (Table 1). Hormonal replacement therapies (HRTs) are indicated for treatment of multiple diseases and were excluded from analysis because it was not possible to differentiate what percentage of the utilization of HRTs was used for each disease. The following HRTs were excluded from analysis: estropipate (approved in 1986), conjugated estrogens (1986), estradiol (1994), conjugated estrogens and medroxyprogesterone acetate (1995), estradiol and norethindrone acetate (1998), ethinyl estradiol and norethindrone acetate (1999), estradiol and norgestimate (1999), estradiol and levonorgestrel (2006), and bazedoxifene acetate and conjugated estrogens (2013).

During the study period, bisphosphonates was the therapeutic subclass with the highest percentage of utilization (Table 2) and also represented the highest market share among other osteoporosis drugs (Figure 1). The utilization of bisphosphonates increased since the approval of alendronate. In the beginning of the study period third quarter of 2006, the utilization of bisphosphonates was 252.6 DDDs per 1000 beneficiaries. The

trends in bisphosphonate utilization in the Medicaid program decreased by 3% annually and reached 218.7 DDDs per 1000 beneficiaries at the end of 2010.

The first-order autoregressive model was selected as the best fit model using AIC. Finding from the ARIMA model indicated a significant decrease in the utilization of bisphosphonates following the issue of the DSC in October 2010 ($p < 0.001$) (Table 3). The DSC resulted in a decrease of 31 DDDs per 1000 beneficiaries per quarter in Medicaid bisphosphonate utilization (95% CI: -14.65 to -52.5, $p = 0.001$).

No such trends were observed for other osteoporosis drugs such as SERMs, teriparatide and calcitonins. The utilization of SERMs decreased from 19.62 DDDs per 1000 beneficiaries in the third quarters of 2006 to 15.77 DDDs per 1000 beneficiaries followed by a decrease in the fourth quarter of 2011 however the trends were not statistically significant ($p = 0.33$).

For SERM, although we can see a decline after the 2010 FDA DSC, there is no statistically significant effect on utilization of SERM after fitting this into ARIMA model (Table 3). Calcitonins had a steady decrease in its utilization at a rate of 5.2% per quarter from 4.4 DDDs per 1000 beneficiaries to 0.71 DDDs per 1000 beneficiaries at the end of study period, and the utilization of teriparatide was shown to decrease by 0.0846 each quarter until the second quarter of 2014. The reduction of calcitonins and teriparatide were not associated with the 2010 FDA DSC ($p = 0.655$, $p = 0.293$) (Figure 2).

Denosumab entered the market as a first-line therapy for patients with severe osteoporosis in June 1, 2010. The utilization of denosumab was 0.04 DDDs per 1000 and increased at a rate of 27% and reached 20.2039 DDDs per 1000 by June 2014. However,

our model indicated that the increase in the utilization of denosumab during the post FDA warning period was not statistically significant (p value= 0.751). This means that the DSC did not affect the utilization of this drug. Among bisphosphonate drugs, alendronate was associated with the highest utilization by Medicaid recipients. All branded and generic bisphosphonates drugs were affected by the 2010 DSC (Figure 3).

Discussion

During the last twenty years, the FDA approved several osteoporosis drugs from five different therapeutic subclasses. In January 1995, only one osteoporosis drug (other than HRTs and calcitonin) was available in the US market. By the end of 2014, the FDA had approved 9 single active ingredients and 2 fixed dose combination drugs.

Study findings reveal a significant change in the pattern of osteoporosis drugs. During the period between 2006 and before the FDA issued the DSC in 2010, we observed a decrease in the utilization of bisphosphonates and other osteoporosis drugs. Previous studies on the use of bisphosphonates observed a significantly decrease in the use of bisphosphonates in the US in patients under 45 years,²⁵ and a decrease in overall osteoporosis drugs post-fragility fracture.²⁶

The safety of bisphosphonate drugs has been addressed in several studies which indicate an association between the long-term use of bisphosphonates and the risk of a atrial fibrillation,²⁷ severe musculoskeletal pain,^{28,29} typical fracture of the femur⁴⁻⁶ and esophageal cancer.³⁰ The FDA has investigated these risks and issued several DSCs on the use of bisphosphonates in the treatment and prevention of osteoporosis.³¹⁻³³ The FDA did not conclude that taking bisphosphonates increases the risk of atrial fibrillation or esophageal cancer. However, the FDA issued a warning regarding atypical fractures with

the long-term use of bisphosphonates. As a result, the FDA required substantial changes in bisphosphonate labels.

In the case of alendronate, the FDA approved a total of 33 supplements including 2 new or modified indications and 22 labeling revisions in the period 2000-April 2014. Alendronate labeling safety revisions were related to the following: gastrointestinal warnings (2002); scleritis and symptomatic hypocalcemia post-marketing adverse reports, and severe skin adverse post-marketing adverse reports (2003); theoretical risk of fetal harm (2004); episcleritis post-marketing adverse reports and osteonecrosis of the jaw precautions (2005); asthenia, dizziness, joint swelling, peripheral edema, and vertigo post-marketing adverse reports (2006); musculoskeletal pain precautions and alopecia post-marketing adverse reports (2008), low-energy femoral shaft and subtrochanteric fractures post-marketing adverse reports, osteonecrosis of the jaw precautions and post-marketing adverse reports, and revision of the warnings related to gastrointestinal adverse events associated with the use of bisphosphonates (2010); and osteonecrosis of the jaw warnings and precautions, and asthma exacerbations post-marketing adverse reports (2013). Additionally, the FDA required a risk evaluation and mitigation strategy (REMS) with information pertaining to the risk of atypical subtrochanteric and diaphyseal femoral fractures with the bisphosphonate drug class in 2010. The FDA decided in 2011 that the REMS for alendronate were no longer required.

In spite of the number of safety label changes, the utilization of alendronate did not significantly change until the 2010 warnings, precautions and REMS. Given that safety actions including warnings, precautions and post-marketing adverse reports released by the FDA before 2010 did not significantly change the use of bisphosphonates,

we hypothesized that the changes in utilization observed after 2010 were related to the implementation of REMS for bisphosphonates that required communications of the risks to patients before starting the therapy.

The 2010 DSC was associated with a significant change in the pattern of utilization of osteoporosis drugs. Although there was an overall decline in the utilization of osteoporosis drugs, our findings indicated that the 2010 DSC only significantly affected the utilization of bisphosphonates. Our regression model points to a delayed effect of the DSC on the utilization of SERMs, as a sharp decline in the utilization of SERMs in Medicaid began in the fourth quarter of 2011, a year after the DSC was released by the FDA. This reduction in SERMs may be due to factors not assessed in this study.

We also noted that the decrease in the utilization of bisphosphonates was associated with an increase in denosumab use in the same period, but our results indicated that this increase was not related to the DSC. This increase may be related to the fact that denosumab is indicated for patients with severe osteoporosis.

The Medicaid population increased during the study period from 33 million in 1995 to 65 million in 2014. The demographic distribution of the Medicaid population also changed during this study period. While women represented around 59% of the total Medicaid population during the entire period of analysis, the percentage of the population aged 65 and older, that are more likely to use osteoporosis drugs, decreased from 12% in 1995 to 8% in 2014.

This study has several limitations. Information about the characteristics of the Medicaid patient population using osteoporosis drugs is not available for analysis of the

impact of FDA DSC on patient care. Also, the utilization of osteoporosis drugs was estimated using DDDs. The DDDs do not represent the actual or FDA approved recommended daily dosages for osteoporosis drugs. Finally, these results relate to the Medicaid program and may not be generalizable to a broader population.

Conclusions

Time series analyses of osteoporosis drug utilization in the Medicaid program showed a significant reduction in the use of bisphosphonates following the 2010 bisphosphonate FDA drug safety communication. This drug safety communication appears to have had a similar effect on other classes of osteoporosis drugs with the exception of denosumab. However, without clinical data, the appropriateness of the effect on this regulatory action is uncertain. Further research may evaluate the effect of the decline in utilization of osteoporosis drugs on fractures.

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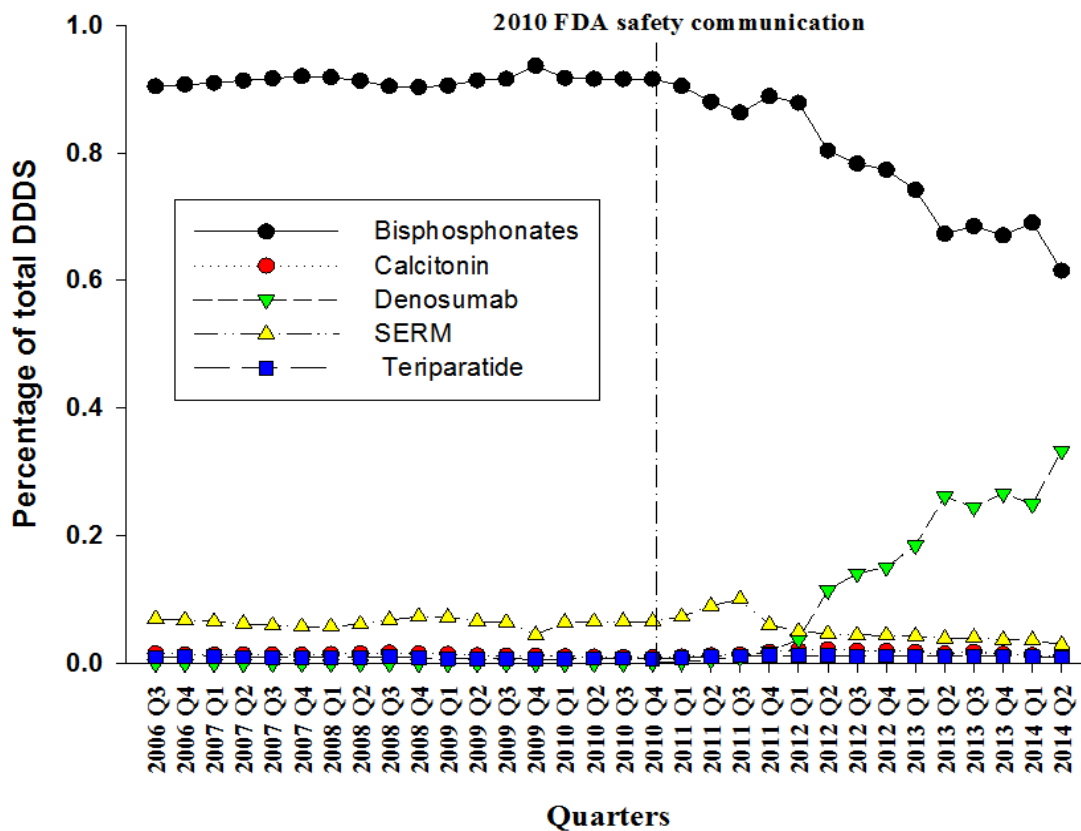


Figure 1. Market Share of Osteoporosis Drug Defined Daily Dose in the Medicaid Fee-For- Service Program (Q3 2006-Q2 2014)

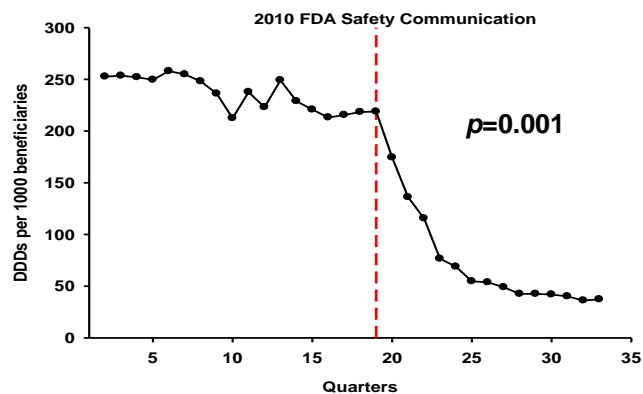
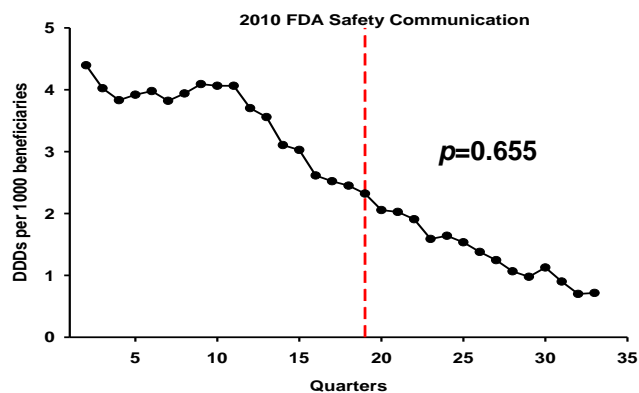
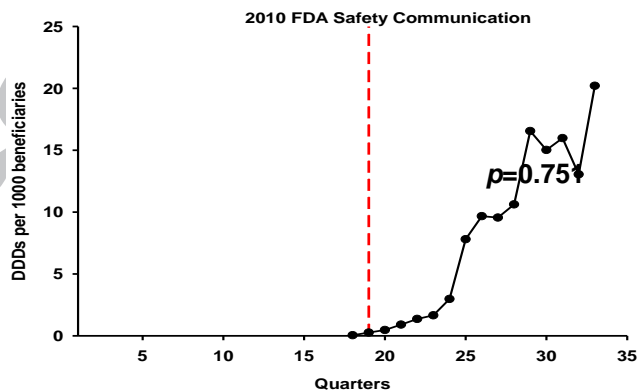
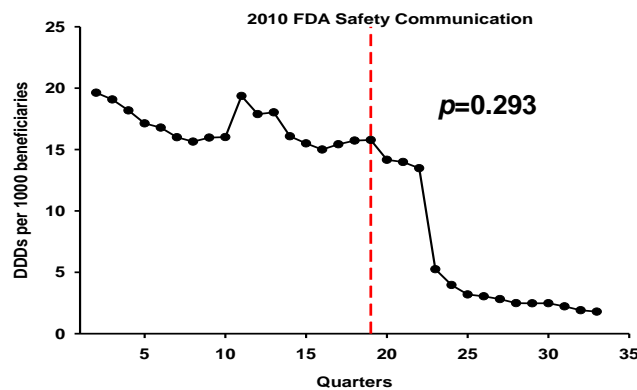
A. Bisphosphonates**B. Calcitonins****C. Denosumab**

Figure 2. Impact of the 2010 FDA Bisphosphonates Safety Communication on the Utilization of Osteoporosis Drugs in the Medicaid Fee-for-Service Program (DDD per 1000 Beneficiaries)

D. SERM



E. Teriparatide

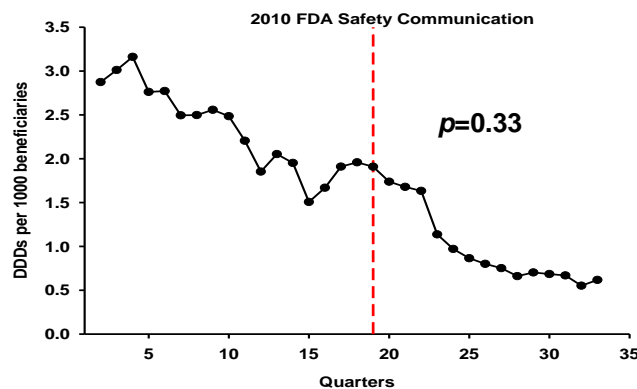


Figure 2. (Continued) Impact of the 2010 FDA Bisphosphonates Safety Communication on the Utilization of Osteoporosis Drugs in the Medicaid Fee-for-Service Program (DDD per 1000 Beneficiaries)

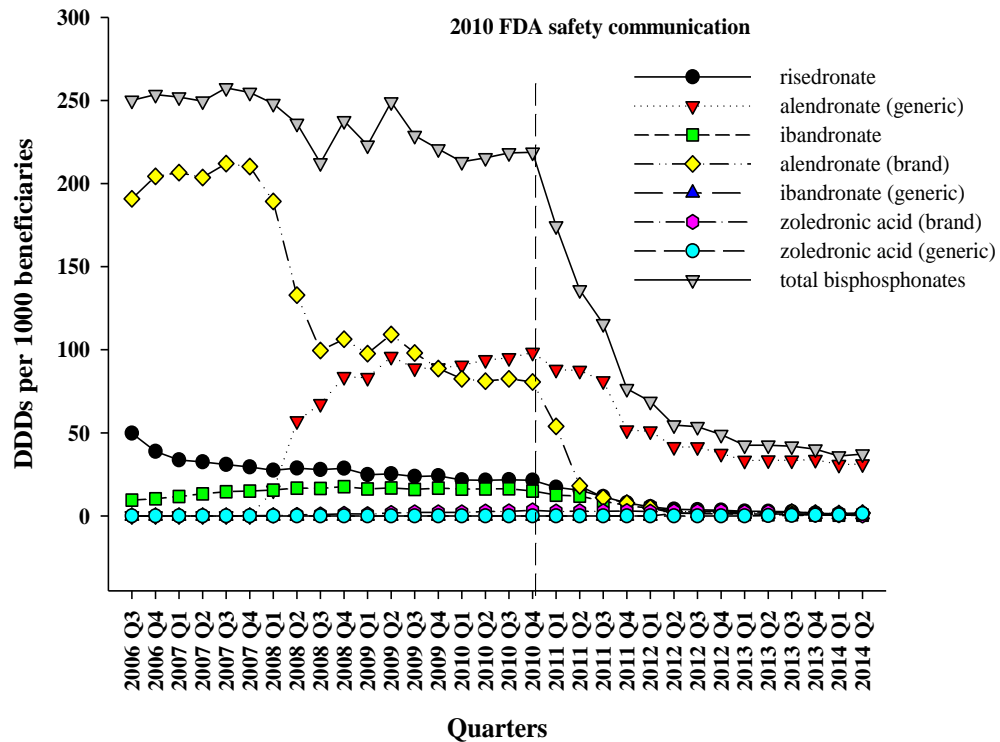


Figure 3. Utilization of Brand and Generic Osteoporosis Drugs in the Medicaid Fee-For-Service Program, DDD per 1000 beneficiaries (Q3 2006 – Q2 2014)

Table 1. List of Osteoporosis Drugs Included in the Study

Chemical Subgroup	Active Ingredient(s)	FDA Approval Year
Bisphosphonates	ibandronate sodium	2003
	zoledronic acid	2007
	alendronate sodium	1995
	risedronate sodium	2000
	alendronate sodium; cholecalciferol	2005
Calcitonins	calcitonin salmon	1995
	calcitonin salmon recombinant	2005
Parathyroid hormones	teriparatide recombinant human	2002
RANKL inhibitors	denosumab	2010
SERM	raloxifene hydrochloride	1997

Table 2. Utilization of Osteoporosis Drugs in the Medicaid Fee-For-Service Program (Q3 2006-Q2 2014)

Year	DDD's per 1000 beneficiaries						Market Share as Percentage of Total DDD				
	Total Utilization	BP	Teriparatide	Calcitonin	SERM	Denosumab	BP	Teriparatide	Calcitonin	SERM	Denosumab
2006	559.1	506.1	5.89	8.42	38.7	-	90.50%	1.10%	1.50%	6.90%	-
2007	1109.18	1014.35	11.19	15.55	68.09	-	91.50%	1.00%	1.40%	6.10%	-
2008	1027.35	934.47	9.74	16.16	66.98	-	91.00%	0.90%	1.60%	6.50%	-
2009	1005.16	921.89	7.36	13.39	62.51	-	91.70%	0.70%	1.30%	6.20%	-
2010	945.44	865.86	7.45	9.9	61.92	0.31	91.60%	0.80%	1.00%	6.50%	0.00%
2011	567.72	502.72	6.18	7.58	46.86	4.38	88.60%	1.10%	1.30%	8.30%	0.80%
2012	278.41	226.23	3.39	5.8	13	30	81.30%	1.20%	2.10%	4.70%	10.80%
2013	241.93	167.34	2.72	4.07	9.65	58.16	69.20%	1.10%	1.70%	4.00%	24.00%
2014	112.92	73.39	1.17	1.42	3.69	33.25	65.00%	1.00%	1.30%	3.30%	29.40%

Table 3. Impact of the FDA Safety Communication on Bisphosphonate Utilization

Model	Intervention	Adjusted for	^a Coefficient	SE	t	^b P value	
ARIMA (1,0,0)	2010_FDA	Women Aged					
			Bisphosphonates	-30.948	8.184	-3.781	0.001
			Calcitonins	-0.053	.117	-.452	.655
			SERM	-1.625	1.516	-1.072	.332
			Teriparatide	-0.149	.132	-1.129	.293

*The model was adjusted for percentage of elderly and women in Medicaid program.

^aCoefficient= utilization changed after the intervention take place

^bStatistical significant set at p value <0.05