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Comments

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Original article

Changes in the utilization of osteoporosis drugs after the 2010 FDA bisphosphonate drug safety communication

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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.

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1. 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 (Wysowski and Greene, 2013). 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 (U.S. Food and Drug Administration, 2014a,b).

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Several studies indicated the association between the long-term use of bisphosphonates and the risk of atypical fracture of the femur (Lenart et al., 2008; Shane et al., 2010; Abrahamsen et al., 2009). 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 3–5 years of use," on the label of all bisphosphonates approved for the treatment of osteoporosis (U.S. Food and Drug Administration, 2014c). In addition, a medication guide should be given to the patient with each bisphosphonate prescription describing the risk and symptoms of these fractures (U.S. Food and Drug Administration, 2014c). 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) (U.S. Food and Drug Administration, 2014c).

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Despite the high prevalence and economic burden of osteoporosis, the literature on the utilization and spending on osteoporosis drugs is scarce (Lee et al., 2006; Udell et al., 2006). 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.

2. Material and methods

2.1. 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 (Centers for Medicare and Medicaid Service, 2014).

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 (U. S. Food and Drug Administration, 2014d). 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.

2.2. Data analysis

Drug utilization was measured by the total defined daily doses (DDDs). 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 (World Health Organization, 2013). 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 (Wagner et al., 2002; Ramsay et al., 2003; Biglan et al., 2000). Interrupted time design is one of the strongest quasi-experimental designs to assess the longitudinal effects of an intervention (Ramsay et al., 2003; Biglan et al., 2000).

Autoregressive integrated moving average (ARIMA) techniques are well established in the literature to perform a time series analysis (Veney and James, 1974; Pamer et al., 2010; Dorsey et al., 2010; Niyomnaitam et al., 2014; Cohen et al., 2010). 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 (Cohen et al., 2010; Shumway and Stoffer, 2010; Matowe et al., 2003).

Osteoporosis drug utilization and pharmacy reimbursement were calculated per 1000 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).

3. 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 (Fig. 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 ($p < .001$) (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 , $p = .001$).

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

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 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

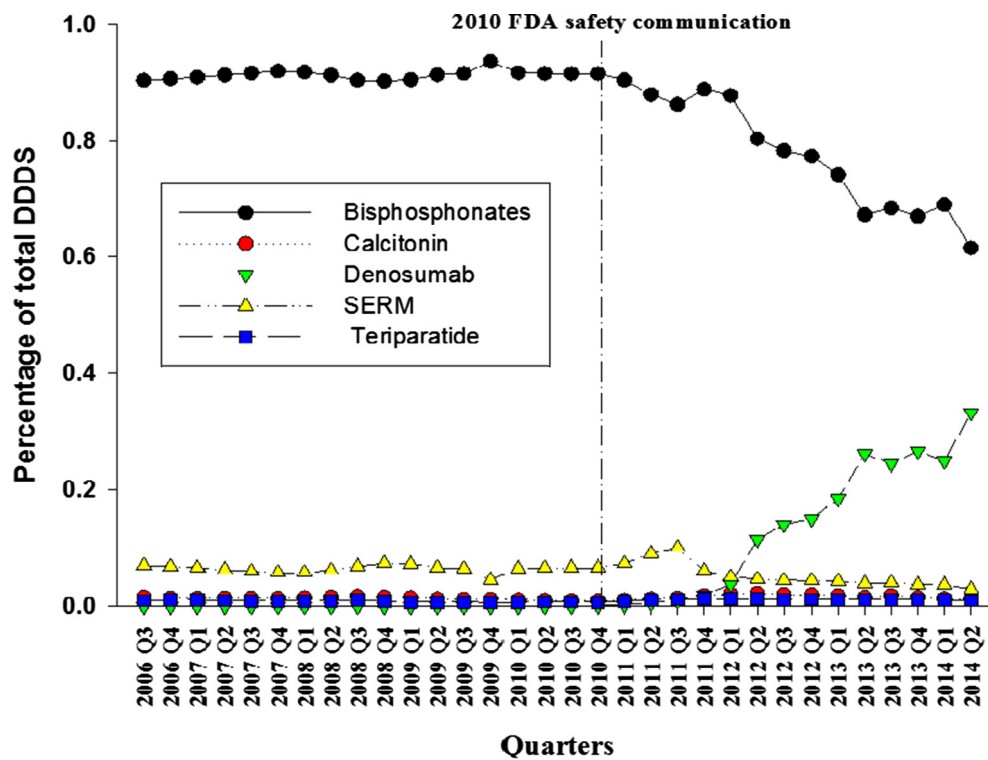


Fig. 1. Market share of osteoporosis drug defined daily dose in the medicaid fee-for-service program (Q3 2006–Q2 2014).

Table 3
Impact of the FDA safety communication on bisphosphonate utilization.

Model	Intervention	Adjusted for	Coefficient ^a	SE	t	P value ^b
ARIMA ^c (1, 0, 0)	2010_FDA	Women, aged				
Bisphosphonates			–30.948	8.184	–3.781	.001
Calcitonins			–0.053	0.117	–0.452	.655
SERM			–1.625	1.516	–1.072	.332
Teriparatide			–0.149	0.132	–1.129	.293

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

^b Coefficient = utilization changed after the intervention take place.

^c Statistical significant set at p value < .05.

by a decreased in the fourth quarter of 2011 however the trends were not statistically significant ($p = .33$).

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 teri-

paratide 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 ($p = .655$, $p = .293$) (Fig. 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,

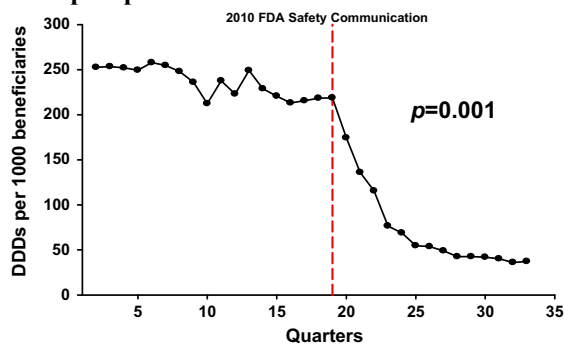
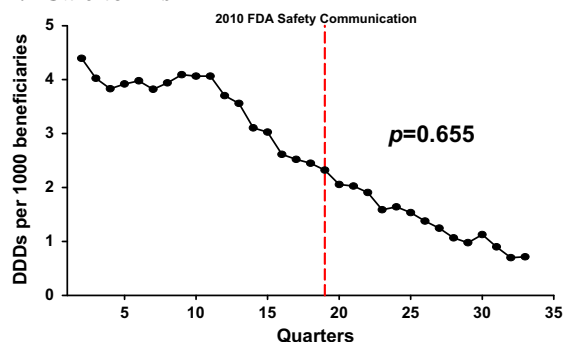
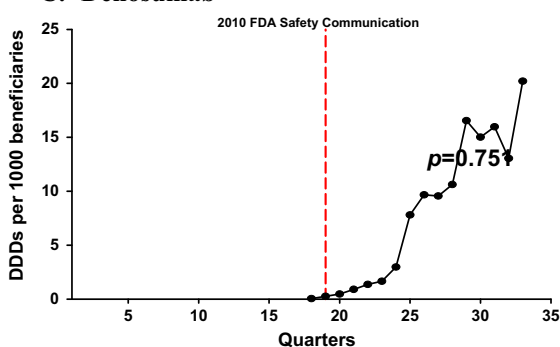
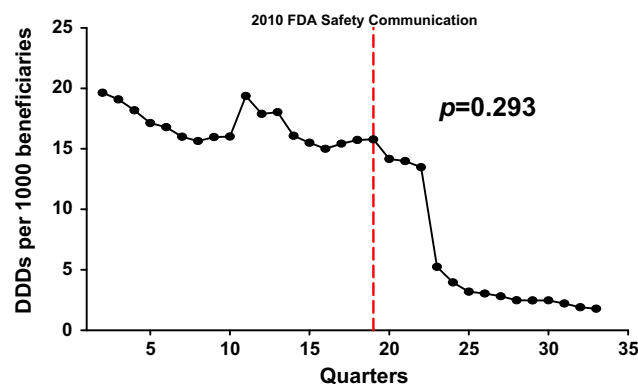
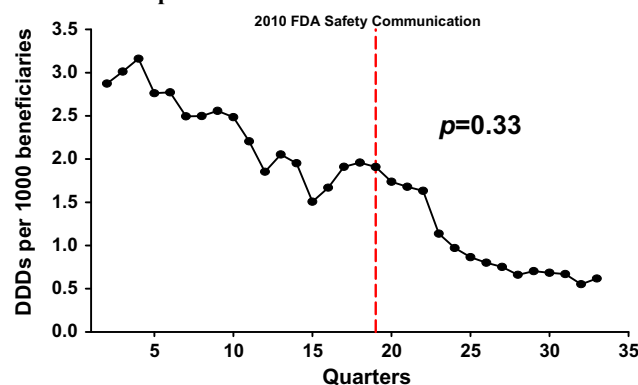
A. Bisphosphonates**B. Calcitonins****C. Denosumab****D. SERM****E. Teriparatide**

Fig. 2 (continued)

Fig. 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).

our model indicated that the increase in the utilization of denosumab during the post FDA warning period was not statistically significant (p value = .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 (Fig. 3).

4. 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 (Xie et al., 2015), and a decrease in overall osteoporosis drugs post-fragility fracture (Balasubramanian et al., 2014).

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 an atrial fibrillation (Cummings et al., 2007), severe musculoskeletal pain (Wysowski and Chang, 2005; Bock et al., 2007), typical fracture of the femur (Lenart et al., 2008; Shane et al., 2010; Abrahamson et al., 2009) and esophageal cancer (Cardwell et al., 2010). The FDA has investigated these risks and issued several DSCs on the use of bisphosphonates in the treatment and prevention of osteoporosis (U.S. Food and Drug Administration, 2008a,b; Bunch et al., 2009). 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 used 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

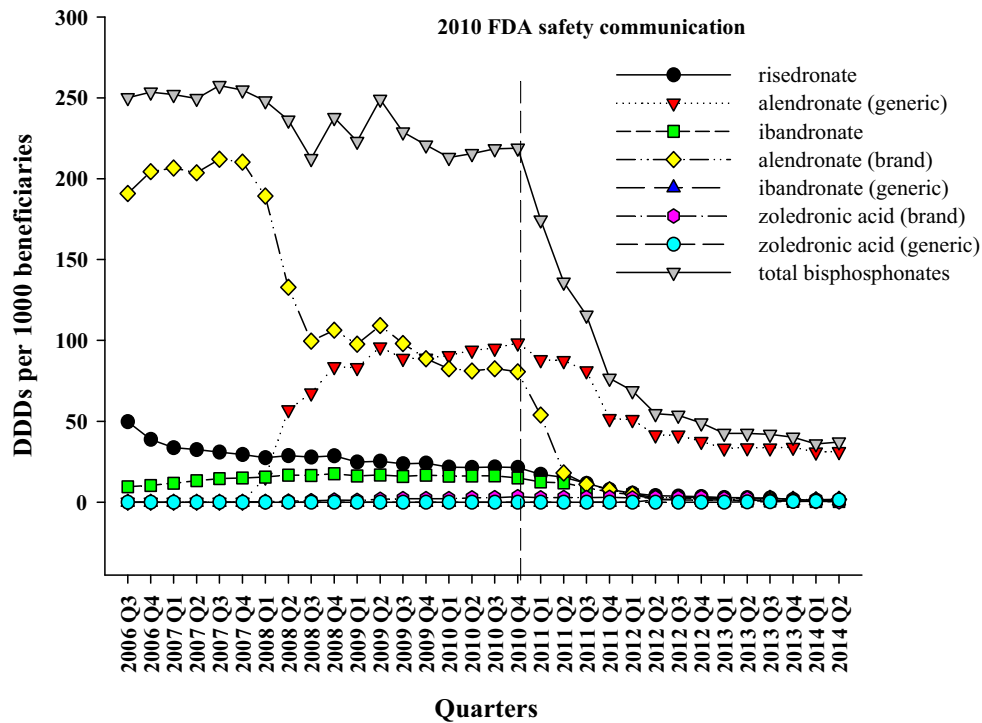


Fig. 3. Utilization of brand and generic osteoporosis drugs in the Medicaid fee-for-service program, DDD per 1000 beneficiaries (Q3 2006–Q2 2014).

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 pertains 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.

5. 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.

References

- Abrahamsen, B., Eiken, P., Eastell, R., 2009. Subtrochanteric and diaphyseal femur fractures in patients treated with alendronate: a register-based national cohort study. *J. Bone Miner. Res.* 24 (6), 1095–1102.
- Balasubramanian, A., Tosi, L.L., Lane, J.M., Dirschl, D.R., Ho, P.R., O'Malley, C.D., 2014. Declining rates of osteoporosis management following fragility fractures in the US, 2000 through 2009. *J. Bone Joint Surg. Am.* 96 (7), e52.

- Biglan, A., Ary, D., Wagenaar, A.C., 2000. The value of interrupted time-series experiments for community intervention research. *Prev. Sci.* 1 (1), 31–49.
- Bock, O., Boerst, H., Thomasius, F.E., et al., 2007. Common musculoskeletal adverse effects of oral treatment with once weekly alendronate and risedronate in patients with osteoporosis and ways for their prevention. *J. Musculoskelet. Neuronal Interac.* 7 (2), 144.
- Bunch, T.J., Anderson, J.L., May, H.T., et al., 2009. Relation of bisphosphonate therapies and risk of developing atrial fibrillation. *Am. J. Cardiol.* 103 (6), 824–828.
- Cardwell, C.R., Abnet, C.C., Cantwell, M.M., Murray, L.J., 2010. Exposure to oral bisphosphonates and risk of esophageal cancer. *JAMA* 304 (6), 657–663.
- Centers for Medicare and Medicaid Service. Medicaid State Drug Utilization Data. <<http://www.medicare.gov/Medicaid-CHIP-Program-Information/By-Topics/Benefits/Prescription-Drugs/Medicaid-Drug-Programs-Data-and-Resources.html>>. Updated 2014 (accessed July 9, 2014).
- Cohen, A., Rabbani, A., Shah, N., Alexander, G.C., 2010. Changes in glitazone use among office-based physicians in the US, 2003–2009. *Diabetes Care* 33 (4), 823–825.
- Cummings, S.R., Schwartz, A.V., Black, D.M., 2007. Alendronate and atrial fibrillation. *N. Engl. J. Med.* 356 (18), 1895–1896.
- Dorsey, E.R., Rabbani, A., Gallagher, S.A., Conti, R.M., Alexander, G.C., 2010. Impact of FDA black box advisory on antipsychotic medication use. *Arch. Intern. Med.* 170 (1), 96–103.
- Lee, E., Wutoh, A.K., Xue, Z., Hillman, J.J., Zuckerman, I.H., 2006. Osteoporosis management in a medicare population after the women's health initiative study. *J. Womens Health* 15 (2), 155–161.
- Lenart, B.A., Lorich, D.G., Lane, J.M., 2008. Atypical fractures of the femoral diaphysis in postmenopausal women taking alendronate. *N. Engl. J. Med.* 358 (12), 1304–1306.
- Matowe, L.K., Leister, C.A., Crivera, C., Korth-Bradley, J.M., 2003. Interrupted time series analysis in clinical research. *Ann. Pharmacother.* 37, 1110–1116.
- Niyomnaitham, S., Page, A., La Caze, A., Whitfield, K., Smith, A.J., 2014. Utilisation trends of rosiglitazone and pioglitazone in Australia before and after safety warnings. *BMC Health Serv. Res.* 14 (1), 151.
- Pamer, C.A., Hammad, T.A., Wu, Y.T., et al., 2010. Changes in US antidepressant and antipsychotic prescription patterns during a period of FDA actions. *Pharmacoepidemiol. Drug Saf.* 158–174.
- Ramsay, C.R., Matowe, L., Grilli, R., Grimshaw, J.M., Thomas, R.E., 2003. Interrupted time series designs in health technology assessment: lessons from two systematic reviews of behavior change strategies. *Int. J. Technol. Assess. Health Care* 19 (04), 613–623.
- Shane, E., Burr, D., Ebeling, P.R., et al., 2010. Atypical subtrochanteric and diaphyseal femoral fractures: report of a task force of the American Society for Bone and Mineral Research. *J. Bone Miner. Res.* 25 (11), 2267–2294.
- Shumway, R.H., Stoffer, D.S., 2010. *Time Series Analysis and its Applications: With R Examples*. Springer Science & Business Media.
- U.S. Food and Drug Administration. Early communication of an ongoing safety review: Bisphosphonates: alendronate (Fosamax, Fosamax plus D), etidronate (Didronel), ibandronate (Boniva), pamidronate (Aredia), risedronate (Actonel, Actonel w/calcium), tiludronate (Skelid), and Zoledronic acid (reclast, zometa) <http://www.fda.gov/Cder/Drug/early_comm/bisphosphonates.htm>. Updated 2008 (accessed March 11, 2015).
- U.S. Food and Drug Administration. Alert. Information on Bisphosphonates (marketed as Actonel, Actonel CA, Aredia, Boniva, Didronel, Fosamax, Fosamax D, Reclast, Skelid, and Zometa) <<http://www.fda.gov/cder/drug/infopage/bisphosphonates/default.htm>>. Published 2008 (accessed January 11, 2015).
- U.S. Food and Drug Administration. Drugs@FDA. <<http://www.accessdata.fda.gov/scripts/cder/drugsatfda>> (accessed July 11, 2014).
- U.S. Food and Drug Administration. Center for Drug Evaluation and Research. FDA Approved Drug Products. <<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>> (accessed May, 22, 2014).
- U.S. Food and Drug Administration. FDA Drug Safety Communication: Safety Update for Osteoporosis Drugs, Bisphosphonates, and Atypical Fractures. <<http://www.fda.gov/Drugs/DrugSafety/ucm229009.htm>> (accessed July 15, 2014).
- U.S. Food and Drug Administration. National Drug Code Directory. <<http://www.fda.gov/cder/ndc>>. Updated 2014 (accessed October 12, 2014).
- Udell, J.A., Fischer, M.A., Brookhart, M.A., Solomon, D.H., Choudhry, N.K., 2006. Effect of the women's health initiative on osteoporosis therapy and expenditure in Medicaid. *J. Bone Miner. Res.* 21 (5), 765–771.
- Veney, J.E., James, W.L., 1974. A comparison of regression and ARIMA models for assessing program effects: an application to the mandated highway speed limit reduction of. *Soc. Indic. Res.* 1983, 83–105.
- Wagner, A.K., Soumerai, S.B., Zhang, F., Ross-Degnan, D., 2002. Segmented regression analysis of interrupted time series studies in medication use research. *J. Clin. Pharm. Ther.* 27 (4), 299–309.
- World Health Organization, 2013. Guidelines for ATC Classification and DDD Assignment. WHO Collaborating Centre for Drug Statistics Methodology, Oslo.
- Wysowski, D.K., Chang, J.T., 2005. Alendronate and risedronate: reports of severe bone, joint, and muscle pain. *Arch. Intern. Med.* 165 (3), 346–347.
- Wysowski, D.K., Greene, P., 2013. Trends in osteoporosis treatment with oral and intravenous bisphosphonates in the United States, 2002–2012. *Bone* 57 (2), 423–428.
- Xie, J., Tong, A., Kim, S.C., 2015. Patterns of bisphosphonates utilization in patients under age 45 in a large cohort of commercial insurance beneficiaries in the United States. *PLoS One* 10 (1), e0115091.