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Analysis of osteoporosis treatment patterns with bisphosphonates and outcomes among postmenopausal veterans

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ABSTRACT

Purpose: Adherence and persistence with bisphosphonates are frequently poor, and stopping, restarting, or switching bisphosphonates is common. We evaluated bisphosphonate change behaviors (switching, discontinuing, or reinitiating) over time, as well as fractures and costs, among a large, national cohort of postmenopausal veterans.

Methods: Female veterans aged 50+ treated with bisphosphonates during 2003–2011 were identified in Veterans Health Administration (VHA) datasets. Bisphosphonate change behaviors were characterized using pharmacy refill records. Patients' baseline disease severity was characterized based on age, T-score, and prior fracture. Cox Proportional Hazard analysis was used to evaluate characteristics associated with discontinuation and the relationship between change behaviors and fracture outcomes. Generalized estimating equations were used to evaluate the relationship between change behaviors and cost outcomes.

Results: A total of 35,650 patients met eligibility criteria. Over 6800 patients (19.1%) were non-switchers. The remaining patients were in the change cohort; at least half displayed more than one change behavior over time. A strong, significant predictor of discontinuation was ≥5 healthcare visits in the prior year (11–23% more likely to discontinue), and discontinuation risk decreased with increasing age. No change behaviors were associated with increased fracture risk. Total costs were significantly higher in patients with change behaviors (4.7–19.7% higher). Change-behavior patients mostly had significantly lower osteoporosis-related costs than non-switchers (22%–118% lower).

Conclusions: Most bisphosphonate patients discontinue treatment at some point, which did not significantly increase the risk of fracture in this majority non-high risk population. Bisphosphonate change behaviors were associated with significantly lower osteoporosis costs, but significantly higher total costs.

Introduction

Poor patient adherence and persistence are common with bisphosphonates, which are considered first-line treatments for postmenopausal osteoporosis (PMO). Reasons for poor adherence and persistence include but are not limited to lack of perceived benefit, lack of understanding, side effects, and inconvenience [1]. In observational studies, the proportions of patients that persisted with therapy for 1 year are low for United States (US) cohorts (21.0–56.7%) and non-US cohorts (21.9–74.8%) [2–11]. Some studies have reported an association between low adherence or persistence and fracture outcomes or healthcare costs (i.e., higher fracture rates or higher costs in patients with lower adherence) [8,12–18]. However, the effect of changing medications on osteoporosis health outcomes has not been well

Abbreviations: BMD, bone mineral density; BMI, body mass index; CDW, corporate data warehouse; COPD, chronic obstructive pulmonary disease; CPT, Current Procedural Terminology; DSS, decision support system; GEE, generalized estimating equations; ICD-9, 9th revision of the International Classification of Diseases; NLP, natural language processing; OLS, ordinary least squares; PCE, Personal Consumption Expenditures; PMO, postmenopausal osteoporosis; SSRIs, selective serotonin reuptake inhibitors; VA, Veterans Affairs; VHA, Veterans Health Administration; VINCI, Veterans INformatics and Computing Infrastructure; WHO FRAX, World Health Organization absolute Fracture Risk Assessment Tool.

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characterized. Several studies demonstrate improved persistence or adherence following a treatment switch [7,19,20], with only one to the contrary [16]. We are aware of one study using a small regional cohort that examined the effect of medication switching on fracture risk. Briesacher and colleagues did not find a significant effect of medication switching on fracture risk in a small sample of patients who switched between once weekly and once monthly bisphosphonates [21]. Given these controversies and inconsistencies in the literature, we sought to examine the effect of switching behaviors on fracture risk and cost outcomes in a large, national cohort of postmenopausal veterans.

Few studies have investigated the link between bisphosphonate medication-taking behavior and osteoporosis-related outcomes while controlling for baseline disease severity. One study restricted analysis to patients with a bone mineral density (BMD) T-score ≤ -2.5 and/or a prior vertebral fracture [14]. However, no studies adjusted for baseline BMD in an effort to isolate the independent effect of adherence on outcomes in patients across a range of osteoporosis severity. This is, perhaps, because most studies that use administrative claims datasets typically do not contain clinical data [11,14–17,20]. However, even studies conducted in datasets containing some clinical data [8,13] still lacked the ability to capture BMD in structured data, making adjustment for baseline disease severity challenging.

To our knowledge, no research has been done to describe bisphosphonate use and outcomes in the female veteran PMO population while controlling for severity. Studies conducted in the Veterans Health Administration (VHA) are usually overwhelmingly male [22,23], and osteoporosis studies have been no exception [24,25]. Thus, in the bisphosphonate-treated PMO population in the VHA, we sought to characterize bisphosphonate switching patterns; to identify patient and disease characteristics that were associated with switching or discontinuation behaviors; and to investigate the possible relationship between patient medication-taking behaviors and outcomes, including cost and fracture events. As a methodological improvement on past observational analyses and a unique feature of our investigation, we used natural language processing (NLP; a computerized algorithm with which certain data or concepts in an electronic text record are identified) to extract information on BMD and other clinical risk factors for fracture from radiology reports and clinic notes. This information was used to control for baseline disease severity [26–28].

Methods

Study design and datasets

In this cohort study, we used historical data from several VHA datasets hosted in the VINCI (Veterans INformatics and Computing Infrastructure) environment, linking across datasets with the VHA's unique scrambled social security number system. Datasets included the VHA's Decision Support System (DSS) dataset, from which we identified bisphosphonate fills, other medications, and cost information for pharmacy, inpatient, outpatient, radiology, and laboratory services; the VHA's Medical SAS dataset, from which we identified age, race/ethnicity, and fracture outcomes; the Corporate Data Warehouse (CDW) dataset, from which we identified vital signs (height and weight for body mass index [BMI] calculation) and narrative records (the clinician progress notes and radiology reports that we used to extract BMD T-scores and other clinical risk factors for fracture).

Natural language processing (NLP)

We used NLP technology to identify several risk factors from narrative text including radiology reports (for BMD) and clinic notes (for BMD, smoking, alcohol consumption, and family/maternal history of osteoporosis or fracture). Separate, narrow-focused NLP applications were built for each of these four variables.

Smoking status was extracted using a system previously developed and validated on the VA clinical notes [27].

Applications to extract the other three variables were built following an iterative system development model, in which a system is built incrementally in phases called iterations. Each iteration consists of planning, development, and error analysis phases. For the current system at each iteration, a set of manually developed rules was built or expanded aiming to detect relevant concepts, their context, and relationships. Iterations involve rigorous error checking to compare system output to manual annotations. The error analysis findings inform the next iteration. The measure of the system performance improvement is estimated by relative decrease in the error rate between iterations. When the error rate improvement falls below 1% it is determined to have reached a plateau and the development cycle is determined to be complete [29].

Final performance of these applications was manually validated on a randomly selected set of notes for each involved variable separately. For example, for the T-score application, a random sample of 1000 instances was reviewed to assess the accuracy of the tool for extracting T-score, anatomy (e.g., anatomic sites mentioned in proximity to the T-score such as lumbar spine or femoral neck), and the association between anatomy and T-score (i.e., that a given site was related in the note to a particular anatomic site, such as a femoral neck BMD T-score versus a lumbar spine BMD T-score). The mean accuracy (number of correct extractions divided by the total number of extractions) of the BMD extraction tool was 82.8% for T-score, 92.6% for anatomic site, and 82.8% for the correct BMD being associated with the correct anatomic site. For smoking, alcohol use, and family/maternal history of osteoporosis or fracture, the mean accuracies were 83.4%, 75.9%, and 76.3%, respectively [26,27].

Previous approaches to acquiring variables for family/maternal history of osteoporosis and BMD scores have used administrative data, personal interviews or questionnaires, manual chart review, [30–33] and prospective measurement [34]. As such, they have been limited to smaller cohorts of patients. Several studies have used NLP to identify family history of other medical conditions or distinguish between family history and personal history, with accuracies ranging from 81.3% to 93.8% [35–37]. Although this range is slightly higher than reported here, each of these studies used only 1 to 2 document types from 1 to 2 hospitals, in which document sections could be specifically identified. Data for our study came from thousands of document types from more than 1400 points of care (medical centers, clinics, nursing homes, and long-care facilities) all across the US.

Alcohol consumption is also usually recorded through interviews, questionnaires, or manual chart reviews [38–40]. Extraction of alcohol consumption status has been attempted using NLP before, with accuracy of 89.4% [41]. The authors admit that such a high level of accuracy is partially attributable to the high level of consistency in the clinical notes in the sample — the same physician dictated them all.

Smoking status has been classified using NLP in several studies, ranging from 23% to 81% [42]. Our system performance is comparable to these previous systems.

Patients

We identified a national cohort of female veterans aged 50 years and older who had an outpatient encounter and who received an osteoporosis bisphosphonate prescription (oral alendronate, oral or injectable ibandronate, oral risedronate, or injectable zoledronic acid) during the study period (January 1, 2003–December 31, 2011). All patients with an outpatient encounter during the study period and then a bisphosphonate prescription at least 6 months later but still within the study period (i.e., the index prescription) were eligible for analysis and were classified as incident or prevalent bisphosphonate users. The index date was defined, not as the first bisphosphonate prescription filled during the study period, but as the first bisphosphonate prescription filled at least 6 months after the first VHA outpatient encounter in the study period. Prevalent bisphosphonate users were those with any bisphosphonate prescription between the beginning of the study period (January 1,