

# Patient Outcomes in the Years After a DXA-BMD Treatment Monitoring Test: Improved Medication Adherence in Some, But Too Little Too Late

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## ABSTRACT

The role of mid-treatment monitoring dual-energy X-ray absorptiometry–bone mineral density (DXA-BMD) for bisphosphonate-treated patients with osteoporosis remains unsettled. A common reason for such monitoring is to encourage ongoing medication adherence. We sought to determine if a DXA-BMD treatment monitoring test was associated with improved medication adherence and whether improved adherence after a DXA-BMD treatment monitoring test was associated with subsequent reduction in fracture rates. Using linked administrative databases within Manitoba, Canada, we performed a retrospective cohort study of women starting and continuing antiresorptive therapy in whom a mid-treatment DXA-BMD monitoring test was performed. From the provincial pharmacy database, we estimated medication adherence by calculating annual medication possession ratio (MPR) and determining the change in MPR with respect to change (stable/decrease) in the DXA-BMD monitoring test, in addition to fracture rates before and after the test. The cohort comprised 3418 women, 90.7% treated with oral bisphosphonate, with pharmacy data for the 3 years before and after the mid-treatment DXA-BMD. Median (interquartile range) MPR was 0.84 (0.49–0.99) in the year before DXA-BMD and 0.84 (0.48–0.99) in the year after DXA-BMD ( $p = 0.37$ ). Among those whose DXA-BMD declined, MPR in the prior year was 0.54 (0.04–0.92) but improved to 0.70 (0.31–0.92) in the year after DXA-BMD ( $p < 0.001$ ). Among those whose DXA-BMD monitoring test was stable/improved, the fracture rate before the monitoring DXA-BMD was 10.1 per 1000 person-years and in those whose DXA-BMD monitoring test showed a decrease, the rate was 23.7 per 1000 person-years ( $p < 0.001$ ). Despite improved adherence in those with DXA-BMD decline, the post DXA-BMD fracture rate was 22.4 per 1000 person-years versus 12.9 per 1000 person-years in those who had stable DXA-BMD ( $p < 0.001$ ). A mid-treatment DXA-BMD reassessment strategy may be useful to focus attention upon adherence, but for optimal fracture outcomes, treatment adherence should be specifically addressed at the commencement of therapy. © 2021 American Society for Bone and Mineral Research (ASBMR).

**KEY WORDS:** DXA; OSTEOPOROSIS; GENERAL POPULATION STUDIES; FRACTURE PREVENTION; ANTIRESORPTIVES

## Introduction

There is considerable controversy as to whether osteoporotic patients using antiresorptive therapy such as bisphosphonates should undergo repeat dual-energy X-ray absorptiometry–bone mineral density (DXA-BMD) as a means of monitoring their treatment. To date, there have been no randomized clinical trials that compare various approaches to DXA-BMD therapy monitoring for the purpose of determining the best approach for reducing fractures in a treated population. Many, but not all,<sup>(1,2)</sup> prior studies, including post hoc analyses of major controlled clinical trials<sup>(3,4)</sup> and observational cohorts,<sup>(5)</sup> have shown that the direction of observed changes in DXA-BMD correlate with overall fracture risk reduction, although the

magnitude of the DXA-BMD-linked contribution may be modest.<sup>(6,7)</sup> We have previously demonstrated a lower fracture rate among those treated patients whose physician performs a DXA-BMD treatment monitoring test compared with those who do not get a DXA-BMD monitoring test.<sup>(8)</sup> There are limited data to suggest that high-risk patients may benefit from a switch to anabolic therapy,<sup>(9,10)</sup> which would be an attractive response to observed DXA-BMD bone loss on therapy if truly due to antiresorptive drug failure, but cost considerations frequently make this an impossibility.

Nonetheless, in the absence of clear evidence as to how to optimally manage the osteoporosis patient with DXA-BMD loss occurring on treatment, some guidelines have argued that a monitoring DXA-BMD should not be performed at all.<sup>(11)</sup> This

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guidance runs counter to both patient and physician desire for a treatment biomarker and a frequent counter-argument claim that some form of patient monitoring could be used to enhance treatment adherence,<sup>(12)</sup> a necessary prerequisite for treatment efficacy.<sup>(13)</sup>

We sought to explore the relationship of treatment outcomes to DXA-BMD treatment monitoring in a real-world context where patient adherence behaviors and fracture outcomes could be examined with reference to the time intervals preceding and following a DXA-BMD monitoring test result. This approach would better reflect the lived experience of the patient and treating physician and inform treatment expectations around the results of a DXA-BMD treatment monitoring test. We hypothesized that among antiresorptive-treated patients, adherence to therapy would improve after physicians and patients received the results of an interim monitoring DXA-BMD but wanted to determine whether any observed improvement in adherence would “rescue” the overall expected fracture risk reduction of an entire treatment course.

## Materials and Methods

We conducted a retrospective analysis within the Manitoba Bone Density Program database, a large, well-known, and well-validated database composed of all DXA-BMD examinations performed in the Canadian province of Manitoba. Since 1995, this database has had patient-level linkage to provincial pharmacy records and other health outcomes including fractures. Altogether, the Manitoba Bone Density Program provides a very long-term, comprehensive data set that integrates clinically relevant information pertaining to the diagnosis, treatment, and monitoring of osteoporosis in a population of 1.3 million persons.<sup>(14)</sup> The DXA-BMD and pharmacy records have been validated and shown to have a 99% rate of completeness and accuracy for all Manitoba residents.<sup>(15,16)</sup> Linked fracture data have also been ascertained according to hospital diagnosis data and diagnosis and service codes in physician billing records with validation of the case definitions against radiological review and fracture rates from the Canadian Multicentre Osteoporosis Study (CaMos).<sup>(17,18)</sup> Analyses were based upon hip, clinical vertebral, forearm, and humerus fracture diagnostic codes (collectively designated “major osteoporotic fractures”) up to March 31, 2018. To minimize potential misclassification of prior incident fractures, we conservatively required that there be no

hospitalization or physician visits with the same fracture type in the 6 months preceding an incident fracture diagnosis. Fractures associated with diagnosis codes indicating high trauma were excluded.

### Medication possession ratios before and after a monitoring DXA-BMD

To examine the real-world associations between a mid-treatment DXA-BMD and subsequent anti-fracture medication adherence, a cohort was constructed that consisted of postmenopausal women aged 50 years or older who commenced therapy after having a DXA-BMD test performed, where therapy commencement was defined as the first prescription of an approved non-estrogen anti-fracture medication (oral or parenteral bisphosphonate, raloxifene, denosumab, calcitonin, teriparatide) without any prior prescriptions. Women were included in the analysis if they had a subsequent DXA-BMD (the “DXA-BMD monitoring test”) measured within 5 years after starting therapy and with anti-fracture medication continuing to be dispensed after the date of the monitoring DXA-BMD. We also required at least 2.5 years of prescription drug data before and after the monitoring DXA-BMD. After being identified for the study cohort, according to the date of the DXA-BMD monitoring test, each woman’s prescription records were traced both backward and forward through the pharmacy database in 12-month intervals to capture up to 3 years of prescription-dispensing data both preceding and following the DXA-BMD test. The medication possession ratio (MPR) for each of the 6 years (3 before and 3 after the DXA-BMD test) was calculated as the total number of days for that interval covered for the dispensed medication divided by the total number of days (365 days for a complete year, proportionately reduced for incomplete years). Although an indirect measure of patient behavior, a higher MPR suggests better medication adherence. Exploratory MPR subgroups were stratified according to the presence or absence of a fracture prior to the DXA-BMD test, age ( $\geq 65$  versus  $< 65$  years old), high FRAX fracture risk status (major osteoporotic fracture risk  $\geq 20\%$  versus 10% to 19%), and therapeutic BMD response (decrease versus no decrease). Finally, sensitivity analyses were performed wherein the study cohort was restricted to women with a full 2 years or 3 years of prescription data both before and after the DXA-BMD monitoring test.

### Early versus late fractures in a treatment course

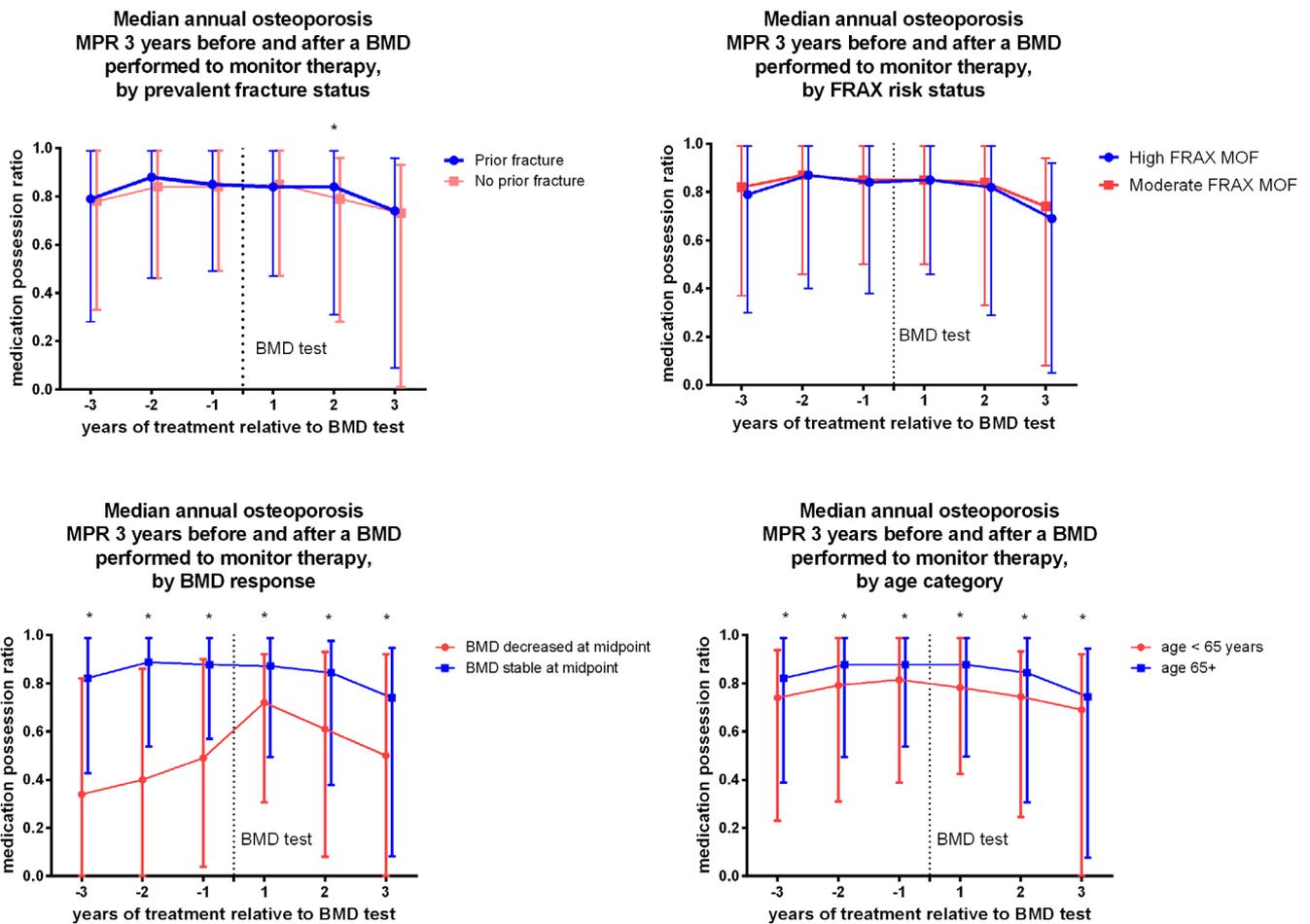
To estimate the associations of therapy MPR and DXA-BMD change during early and later phases of treatment upon fracture occurrence but without the confounding of a change in treatment agent, we restricted the cohort to those in whom there was no therapy change. We also excluded those with significant glucocorticoid or aromatase inhibitor use (exceeding 90 days). Patients were grouped into two categories according to whether their mid-treatment DXA-BMD had shown stability or significant decrease. A significant decrease in DXA-BMD was defined as a decrease at either lumbar spine or total hip that exceeded the 95% least significant change for the DXA program (0.05 and 0.03 g/cm<sup>2</sup>, respectively). The DXA-BMD monitoring test was considered to effectively divide the total treatment course into an early phase (treatment initiation to first DXA-BMD monitoring test) and late phase (continued treatment for a matching time duration post DXA-BMD monitoring test). We then counted

**Table 1.** Cohort Characteristics at the Time of DXA-BMD Monitoring Test

Characteristic	N = 3418
Age (years)	69.1 ± 8.5
Body mass index (kg/m <sup>2</sup> )	25.2 ± 4.4
Prior fracture (%)	935 (27.4)
Femoral neck T-score	-1.9 ± 0.7
Minimum T-score	-2.5 ± 0.8
Minimum T-score ≤ -2.5	1695 (49.6)
Major osteoporotic fracture risk (%) <sup>a</sup>	14.0 ± 7.7
Major osteoporotic fracture risk $\geq 20\%$ <sup>a</sup>	610 (17.8)

DXA-BMD = dual-energy X-ray absorptiometry–bone mineral density. Data are mean ± SD or n (%).

<sup>a</sup>Major osteoporotic fracture risk calculated using FRAX (Canadian version) with BMD.



**Fig. 1.** Median osteoporosis medication possession ratios (MPR) before and after a mid-treatment dual-energy X-ray absorptiometry–bone mineral density (DXA-BMD), stratified according to whether the woman had a history of fracture, high fracture risk by FRAX, significant decrease in the mid-treatment DXA-BMD, or age older versus younger than 65 years. \*Indicates statistically significant non-paired between-group difference for presence versus absence of clinical factor. Error bars are interquartile ranges.

incident major osteoporotic fractures occurring in both phases, according to DXA-BMD change (BMD decrease versus stability/increase).

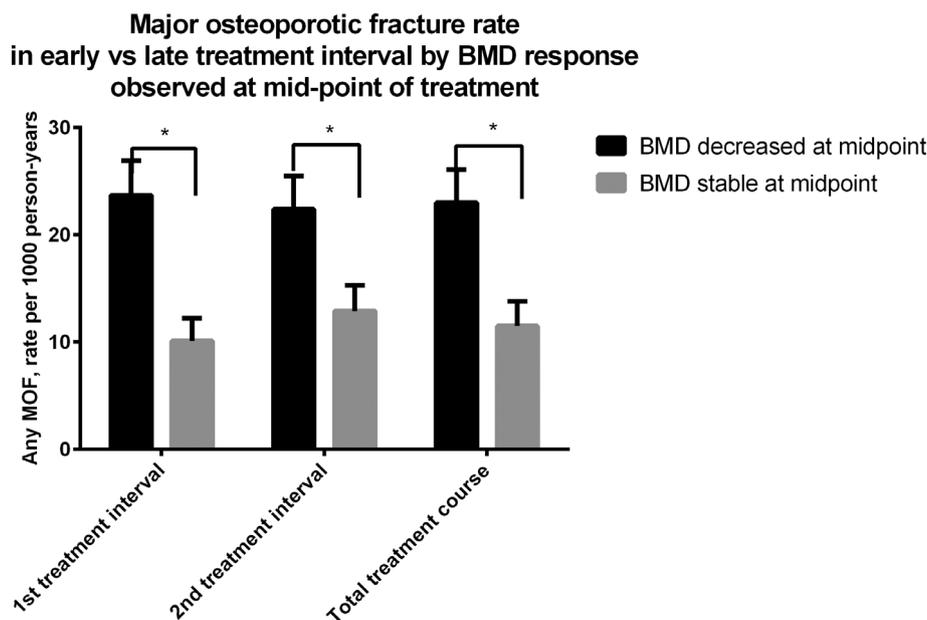
### Statistical analyses

The characteristics of the study cohort were described using means, standard deviations (SDs), frequencies, and percentages. Nonparametric Mann–Whitney tests were used to compare non-paired MPR data between subgroups (eg, with versus without prior fracture) and Wilcoxon signed-rank tests were used for paired comparisons within subgroups (ie, MPR in the year before versus year after DXA-BMD). Poisson confidence intervals were calculated for comparison of population fracture rates, expressed as events per 1000 person-years observation. Statistica version 13.0 (Statsoft Inc, Tulsa, OK, USA) and MedCalc 19.0.7 (MedCalc Software bvba, Ostend, Belgium) were used for all analyses, and  $p < 0.05$  was used to assess statistical significance.

### Results

For the primary MPR analysis, there were 3418 women whose records met the study inclusion criteria (Table 1; Supplemental Fig. S1). The mean (SD) age was 69.1 (8.5) years and 25.2% had a prior history of low-trauma fracture. The mean (SD) femoral neck  $T$ -score was  $-1.9$  (0.7) and 49.6% had a  $T$ -score of  $< -2.5$  for at least one of the hip and/or spine BMD measurements. The mean FRAX score for 10-year major osteoporotic fracture risk (Canadian) was 14% (7.7). The osteoporosis treatment used was a bisphosphonate in 90.7% of the women. Within the subgroup MPR analyses, there were 935 women (27.4%) who had a history of fracture before the mid-treatment DXA-BMD, 610 women (17.8%) whose initial FRAX score was  $\geq 20\%$ , and 424 women (12.4%) in whom the DXA-BMD monitoring test showed a significant decrease.

For the overall cohort, there was no change in MPR after the DXA-BMD monitoring test: 0.84 (0.49–0.99) in the year before DXA-BMD and 0.84 (0.48–0.99) in the year after DXA-BMD ( $p = 0.37$ ). Fig. 1 shows the before and after DXA-BMD



**Fig. 2.** Major osteoporotic fracture rate (MOF) per 1000 person-years in treated women according to whether their mid-treatment dual-energy X-ray absorptiometry–bone mineral density (DXA-BMD) showed stability or decrease. Error bars are 95% confidence intervals, \* $p < 0.05$ .

monitoring data regarding MPR in subgroups of interest (numeric data in Supplemental Table S1). Median MPR was similar between women with versus without a prior fracture, with a small difference found only for the second year after DXA-BMD monitoring (0.84 versus 0.79, respectively;  $p = 0.018$ ). Women age 65 years or older had significantly higher MPR at all time points compared with those under age 65 years (all  $p < 0.05$ ) but without change after the DXA-BMD monitoring test. Among patients at high 10-year fracture risk ( $\geq 20\%$ ), MPR was not significantly different compared with patients at moderate risk (10% to 19%). The most striking observations were found in the analysis of MPR according to the results of the DXA-BMD monitoring test. There was a large difference in MPR in the year immediately before the DXA-BMD monitoring test for patients with BMD loss versus stability (0.49 versus 0.88, respectively;  $p < 0.001$ ). Among those with DXA-BMD loss, there was a significant improvement in the MPR for the year after the DXA-BMD monitoring test ( $p < 0.001$ ), but this remained below the MPR for those with stable DXA-BMD (0.72 versus 0.87, respectively;  $p < 0.001$ ) and rapidly declined to 0.61 in the second year and 0.50 in the third year after DXA-BMD. The results of the sensitivity analyses are shown in Supplemental Tables S2 and S3, where it may be observed that use of a cohort defined by full 2- or 3-year follow-up prescription data did not change the results of the primary analysis.

The relationship between overall fracture rates before and after DXA-BMD monitoring test are shown in Fig. 2. Among those with stable DXA-BMD at the midpoint, the first interval fracture rate was 10.1 per 1000 person-years versus 23.7 per 1000 person-years among those whose DXA-BMD showed significant decrease, for an absolute difference of 13.6 (95% confidence interval [CI] 10.0–17.2,  $p < 0.001$ ) per 1000 person-years and a fracture incidence rate ratio 2.34 (95% CI 1.85–2.99,  $p < 0.001$ ). Despite the modestly improved post-DXA-BMD MPR in the group with observed bone loss, the fracture rate during

the post-DXA-BMD interval was 22.4 per 1000 person-years compared with 12.9 per 1000 person-years in those whose DXA-BMD had been stable (and with MPR higher from the start), for an absolute difference of 9.5 (95% CI 5.8–13.2) per 1000 person-years and a fracture incidence rate ratio of 1.73 (95% CI 1.39–2.17,  $p < 0.001$ ). Across the entire treatment course (the 3 years before and after DXA-BMD monitoring test), the subgroup with mid-treatment bone loss sustained twice as many fractures (incidence rate ratio 2.0, 95% CI 1.6–2.52;  $p < 0.001$ ) compared with those with stable BMD.

## Discussion

Studies of the use of DXA-BMD to monitor bisphosphonate therapy present a unique paradox; while the scientific validity of numeric trends found in paired DXA-BMD measures for an individual patient may be uncertain,<sup>(5,19,20)</sup> the performance of the test was associated with a change in patient behavior as pertains to estimated medication adherence among those whose DXA-BMD appeared to decrease. On the other hand, among women whose mid-treatment DXA-BMD was stable, there was no improvement in good adherence, based on median medication possession ratios of 0.82 to 0.88 in the years leading up to DXA-BMD testing. An observed decrease in DXA-BMD while on therapy or early fracture on therapy proved to be strongly associated with subsequent higher fracture risk. Thus, it may be observed that the patient who did poorly in the first years of treatment due to suboptimal medication adherence could be readily identified by DXA-BMD monitoring and yet despite the subsequent positive change in behavior, the elevated fracture rate observed afterward suggests that it is too little improvement, too late to fully rescue the originally anticipated benefits of therapy.

The central theme of our study reflects the problem of early nonadherence to anti-fracture therapy, its detection, and its consequences in terms of fracture outcomes. The goal of osteoporosis therapy is to reduce or delay the appearance of fractures, and this is highly dependent upon patient medication adherence. A prior study has shown that among several common chronic diseases, medication adherence in osteoporosis may be one of the poorest.<sup>(21)</sup> Pooled estimates in a meta-analysis of oral osteoporosis therapies suggested overall adherence rates of 42% to 52% for treatment durations up to and beyond 24 months,<sup>(22)</sup> starting from the very first prescription onward. This suboptimal medication use has been shown to be associated with significantly higher fracture rates.<sup>(23)</sup> A meta-analysis of more than 170,000 patients receiving short-term (<3 years) bisphosphonate therapy suggested an overall 46% increase in the risk of clinical fractures among less-adherent patients compared with more ideal adherence.<sup>(24)</sup> Siris and Briesacher each reported that there may be no fracture benefit at all when medication MPR figures are below 50% to 60%.<sup>(25,26)</sup> Our study adds to the understanding of the impact even variable adherence plays over the entire course of a monitored bisphosphonate treatment. When poor clinical response (ie, decreasing DXA-BMD) was discovered and (presumably) shown to the patient, medication adherence improved modestly (although still not equivalent to those in whom BMD did not decrease) and yet subsequent fracture rates remained much higher than those who had been medication-adherent from the start.

Strategies shown to improve osteoporosis therapy adherence include less frequent dosing of medications,<sup>(27,28)</sup> but even these strategies, including intermittent parenteral therapies, have weaknesses in that they may require more complex arrangements outside the physician's office, which impedes long-term continuation.<sup>(29)</sup> Previous studies of osteoporosis therapy persistence have found that poor persistence among patients is often attributable to both fear of adverse effects as well as actual perceived adverse effects, in addition to self-reported insufficient motivation to continue treatment.<sup>(30)</sup> More regularly scheduled osteoporosis-specific follow-up visits with a health professional may be beneficial for improving adherence and persistence with therapy.<sup>(31)</sup> Use of a fracture liaison service may also be considered, although even with this focused intervention, treatment persistence may decline to less than 80% beyond 2 years.<sup>(32)</sup> The importance of patient education has been stressed in prior interventions to improve adherence,<sup>(33)</sup> with modest effect. More recently, a specific focus on patient autonomy and shared decision-making in osteoporosis group medical visits has demonstrated the potential for very high treatment adherence at 1 year<sup>(34)</sup> with the explanation that women will be more likely to take and persist with a medication that they themselves wanted to initiate, after getting substantial education and support.

Clinical patient monitoring has been previously shown to significantly improve medication adherence in a small randomized trial of 75 postmenopausal women with osteopenia<sup>(12)</sup> and in a larger randomized study using bone turnover markers.<sup>(35)</sup> Our data partially confirm this principle by showing that a beneficial adherence effect may be found in the small subset of women (12%) whose monitoring DXA-BMD detects a decrease. However, across the entire cohort, BMD monitoring did not appear to have any association with improved medication possession ratios. Confounding the situation for individual patients is the fact that serial DXA-BMD may be prone to artifacts in measurement and/or reporting<sup>(36)</sup>; spurious or irreproducible apparent

changes are commonly found, likely because of greater-than-appreciated precision error.<sup>(37)</sup> Patients do not always understand or correctly interpret the information given about their DXA-BMD,<sup>(38)</sup> which may cause confusion in their decisions around therapy initiation or adherence. We have previously published that there is better medication adherence (and fewer fractures) in patients who receive any BMD monitoring than in those who do not,<sup>(8)</sup> but it was uncertain as to whether this was in response to a specific DXA-BMD result or whether the occurrence of any DXA-BMD monitoring was simply a marker of a higher degree of attention being paid to many possible facets of osteoporosis management at the health professional level. Our present analysis extends this observation to show that the improved MPR does indeed appear to be largely related to a change in behavior among those whose DXA-BMD monitoring test shows decrease, strongly suggesting a patient decision arising from an appreciation that prior poor adherence may have led to the observed BMD losses.

Our analysis has some limitations to be considered. Specifically, we could not assess unique patient-level or physician-specific factors in the administrative databases that may influence treatment adherence and observed changes in MPR with respect to DXA-BMD. Nonetheless, our inclusion of MPR data for 3 years before and 3 years after DXA-BMD allows for a sufficiently long observation window of medication use such that time-specific, dramatic MPR changes (as found with DXA-BMD decreases) may be reasonably linked to the clinical DXA-BMD-performed at that time. As a retrospective analysis of clinical practice data and not a prospectively defined comparison of different monitoring strategies, the possibility of additional confounding by indication or other unknown clinical factors remains a possibility. Finally, prescription dispensation is not necessarily commensurate with medication ingestion. Pill counts or direct observed therapy is an advantageous approach but would require primary data collection in a prospective study.

In conclusion, our study of real-world osteoporosis medication use relative to DXA-BMD monitoring tests, fractures, and baseline risk factors shows that a decrease detected on DXA-BMD monitoring was associated with a modest improvement in subsequent osteoporosis medication adherence. Unfortunately, improved but late-onset adherence did not restore the subsequent reduction in fracture rate to that which might have been achieved with adherence from the start. Although a mid-treatment DXA-BMD reassessment strategy may be useful to focus attention upon adherence, for optimal fracture outcomes, treatment adherence should be specifically addressed at the commencement of therapy and each visit thereafter.

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All authors declare no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; and no other relationships or activities that could appear to have influenced the submitted work.

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Authors' roles: GAK conceived the study, assisted in the primary analysis, and wrote the first draft of the manuscript. LML both assisted with appraisal/review of the primary analysis and critically appraised and edited the manuscript to its final form. WDL established the database and conducted the primary statistical analysis in addition to critical review of the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. GAK and WDL accept full responsibility for the work and conduct of the study. WDL had access to the data and controlled the decision to publish.

## Peer Review

The peer review history for this article is available at <https://publons.com/publon/10.1002/jbmr.4333>.

## Data Availability Statement

Data sharing is not available under the Researcher Agreement with Manitoba Health, Seniors and Active Living (MHSAL).

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