



## Determinants of Observance to Osteoporosis Treatment in Clinical Practice in a Single Center Study

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### Abstract

**Background:** Improve compliance to prescribed medications is common in clinical practice, and it can lead to potentially fatal outcomes. This continues to be a common issue in the treatment of osteoporosis, although the causes of discontinuation and low compliance are complicated and understudied. **Material & Methods:** A survey was conducted in 101 patients at Narsingdi Sadar Hospital, Narsingdi, Dhaka, Bangladesh for osteoporosis management for a follow-up assessment, one year (July 2020 to June 2021) after having been prescribed a treatment with one of the following drugs: Calcium+vitamin D supplements alone (CaVitD), hormone replacement therapy (HRT), risedronate 5 mg/day (RIS), alendronate (ALN OW), Ibandronic acid monthly and Zolindronic acid I/V inj yearly. **Results:** Overall, 19.1 % stopped taking their prescribed medication before their bone mass reevaluations, with more than half of them doing so within the first 6 months. The dropout rate differed dramatically between regimens. ALN-OW was by far the least interrupted (6.9 %; p0.001 versus any other treatment). The most common causes for cessation were drug-related side effects, a lack of willingness to continue therapy, and a fear of negative effects. The reasons for discontinuation differed by treatment: safety concerns were very common for HRT, lack of motivation was the most common cause for CaVitD and drug-related side effects were the most common cause for RIS, ALN, Ibandronic acid and Zolindronic acid. Patients having a history of vertebral fractures, densito-metric osteoporosis, or who were using corticosteroid or anti-inflammatory medications had a considerably greater rate of treatment adherence. Patients on benzodiazepine or gastroprotective drugs, as well as those for whom a bone measurement was not easily accessible, had a considerably greater probability of treatment interruption. ALN OW and HRT had the highest compliance to recommended dosing (p0.001 versus any other) and CaVitD had the lowest (p0.01 versus any other). Poor treatment compliance (50 percent medicine taken) was strongly associated with benzodiazepine and gastroprotective usage, whereas significantly higher compliance was associated with established osteoporosis risk factors: early menopause, low bone mass values, and past vertebral fractures. Adherence was lowest when treatments were prescribed by general practitioners (GPs) and orthopaedic surgeons (p0.01 compared to the global mean). **Conclusions:** According to the conclusions of this large survey of Bangladeshi osteoporotic women, the kind of medicine provided is the most important factor of both persistence



and compliance to treatment, with ALN-OW having a separate advantage. Treatment is particularly low for CaVitD, suggesting the need for innovative methods of supplementing at least vitamin D. The most common causes for cessation include adverse effects and a lack of motivation, while patients with severe and well-documented osteoporosis would have the maximum medication compliance.

**Keywords:-** Observance, Adherence, Compliance, Osteoporosis, Persistence, Treatment.

## INTRODUCTION

Poor adherence to prescribed treatments is widespread in clinical practice, with reported rates close to 50%, particularly for many chronic conditions considered “clinically silent” to the patient.<sup>[1,2,3]</sup> This can lead to potentially life-threatening events.<sup>[4,5,6,7]</sup> Evidence is accumulating which demonstrates that a substantial proportion of patients abandon current osteoporosis treatments within just 6–7 months of treatment initiation and that the probability of continuing osteoporosis treatment decreases over time.<sup>[8,9,10,11]</sup> The proportion of patients with un-interrupted therapy after 1 year was found to be close to only 20% for any type of anti-resorptive therapy.<sup>[12]</sup> Compliance to prescribed dosing, generally continuing how well a patient follows a physician’s instructions during a specific period, is also often inadequate.<sup>[13]</sup> It has been recognized that the full benefits of medications for osteoporosis cannot be reached if compliance is low. Poorly compliant patients have smaller bone mineral density (BMD) gains, a weaker suppression of bone turnover and, ultimately, a greater risk for fractures than patients who adhere to their prescribed therapy.<sup>[14,15]</sup> The causes of discontinuation and low compliance to medical therapy for osteoporosis in patients treated in

clinical practice are complex and poorly defined, and the rates of both are likely to be worse than those reported in patients participating in clinical trials, where the latter are probably healthier and better counselled than patients in clinical practice.

We report here the rate and possible determinants of poor adherence (persistence and compliance) to osteoporosis treatment in a large number of women prescribed a pharmacological treatment for osteoporosis in a routine clinical setting. The term adherence comprises here both compliance and persistence to treatment. Compliance refers to how the medication is taken or quality of intake. Persistence is defined as the time from initiation to discontinuation of treatment.

## MATERIAL AND METHODS

During a 1 year period the hospital were asked to recruit into the study all consecutive postmenopausal women referred for a control of bone mass who had been prescribed at least 1 year prior to this time one of the pharmacological agents registered for the treatment of osteoporosis in Narsingdi Sadar Hospital, Narsingdi, Bangladesh. After obtaining an informed consent approved by each ethical committee, the patients were asked to complete a questionnaire. The data were

then collected on a specific data collection form or directly on an electronic grid that allowed an initial automatic cleaning of the data by flagging any outlier value. The data were then sent electronically to a web center, which was accessible to all investigators throughout the study period and which is currently accessible to any qualified medical doctor. The patients' demographic and reproductive characteristics recorded at baseline were: age, weight, height, age at menopause, type of menopause (natural, surgical). In addition, details about the following clinical and lifestyle risk factors were collected: history of fragility fractures after age 40 years, history of fragility hip fracture in mother, problems with sense organs (sight, hearing), smoking status, alcohol consumption, regular exercise and mobility status. The presence of concurrent diseases that may increase the risk of osteoporosis or falls was recorded. The following information was obtained on the osteoporosis treatment prescribed at the previous visit: type of drug, specialization of the prescribing doctor, degree of compliance, time and reasons of incidental discontinuation. Given the nature of the study, the data on treatment adherence were exclusively self-reported. The SPSS ver. 24.0 statistical software programme (SPSS, Chicago, Ill.) was used for all statistical analyses. The between-groups differences were analyzed by repeated measures analysis of variance (ANOVA) or by co-variance analyses and then by t-test, with the Bonferroni comparison test applied for multiple comparisons. Logistic regression analysis was used for analyzing the Relative Risk (RR) for treatment discontinuation. Analyses for categorical data related to treatment compliance was performed using the  $\chi^2$ -test.

## RESULTS

Overall, 19.1 % stopped taking their prescribed medication before their bone mass reevaluations, with more than half of them doing so within the first 6 months. The dropout rate differed dramatically between regimens. ALN-OW was by far the least interrupted (6.9 %;  $p < 0.001$  versus any other treatment). The most common causes for cessation were drug-related side effects, a lack of willingness to continue therapy, and a fear of negative effects. The reasons for discontinuation differed by treatment: safety concerns were very common for HRT, lack of motivation was the most common cause for CaVitD, and drug-related side effects were the most common cause for RIS, ALN, and Alandronic acid and Zolindronates. Patients having a history of vertebral fractures, densitometric osteoporosis, or who were using corticosteroid or anti-inflammatory medications had a considerably greater rate of treatment adherence. Patients on benzodiazepine or gastro protective drugs, as well as those for whom a bone measurement was not easily accessible, had a considerably greater probability of treatment interruption. ALN OW and HRT had the highest compliance to recommended dosing ( $p < 0.001$  versus any other) and CaVitD had the lowest ( $p < 0.01$  versus any other). Poor treatment compliance (50 percent medicine taken) was strongly associated with benzodiazepine and gastro protective usage, whereas significantly higher compliance was associated with established osteoporosis risk factors: early menopause, low bone mass values, and past vertebral fractures. Observance was lowest when treatments were prescribed by general practitioners (GPs) and

Orthopaedic surgeons (p0.01 compared to the global mean).

**Table 1:** Referring specialists and the treatment prescribed (percentage by each specialist) for osteoporosis, Number of patients Calcium-vitamin D, Hormones, Alendronate, Risedronate, Ibandronic acid and Zolindronic acid.

	Number of patients	Calcium-vitamin D	Hormones	Ibandronic acid	Zolindronic acid I/V (inj)	Alendronate	Risedronate
Endocrinologist	8	18.2%	4.9%	12.8%	13.2%	40.2%	10.7%
Physiatrist	7	14.2%	0.4%	6.4%	12.6%	55.0%	11.4%
Geriatrician	8	9.6%	0.8%	9.3%	12.2%	53.2%	14.8%
Gynecologist	15	11.1%	51.0%	16.2%	4.2%	14.5%	3.0%
Internist	11	11.8%	1.2%	6.3%	12.0%	57.8%	10.8%
General practitioner	17	31.0%	0.5%	4.0%	35.0%	24.7%	4.8%
Orthopedic surgeon	16	16.5%	0.4%	5.7%	25.0%	40.8%	11.5%
Rheumatologist	14	15.6%	0.8%	5.9%	15.1%	49.6%	13.0%
Others or mix	5	2.4%	3.8%	7.8%	17.8%	59.1%	12.0%
All	101	17.1%	8.1%	7.9%	17.7%	29.8%	9.5%

**Table 2:** Baseline characteristics of the study population according to the assigned treatment: mean and standard deviation (SD).

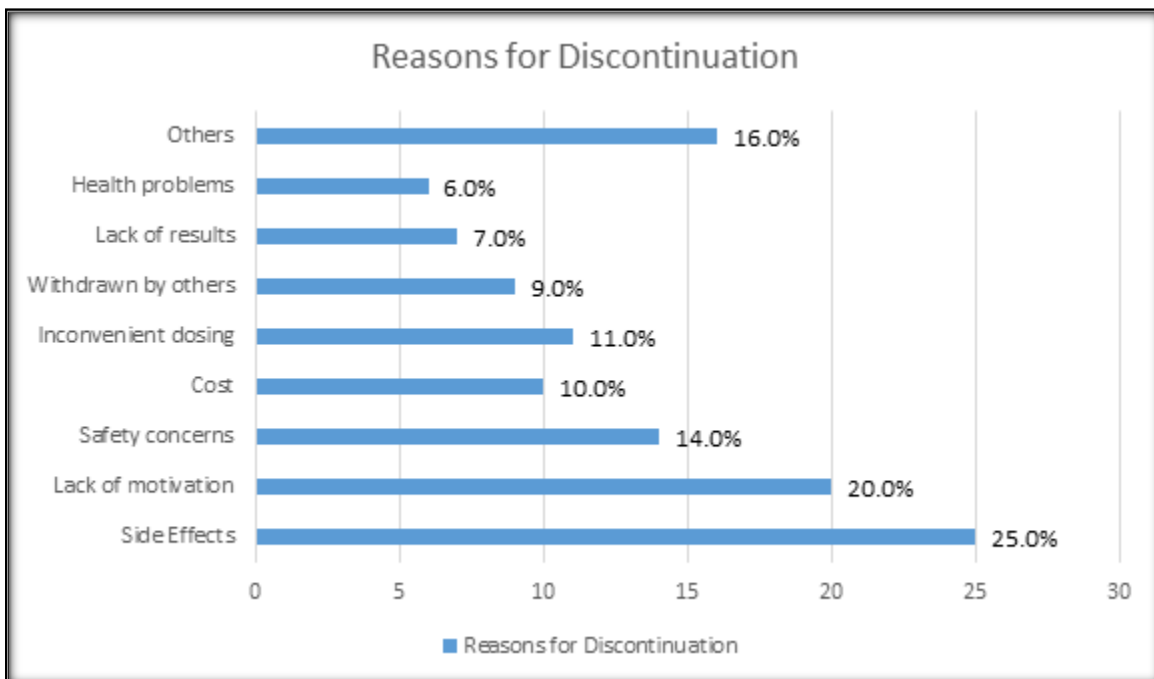
Treatment	Age (years)	Age of menopause (years)	BMI(kg/m <sup>2</sup> )	BMD spine (T-score)	BMD total hip (T-score)	Stiffness QUSCalcaneous(T-score)
Calcium-vitamin D (n=17)	63 (10)*	48 (5)	26.2 (4.5)*	-2.1 (1.1)*	-1.9 (0.9)*	-2.0 (1.1)*
Hormone replacement therapy (n=8)	55 (6)*	47 (6)	24.4 (3.7)*	-1.7 (1.3)*	-1.2 (1.2)*	-1.4 (0.8)*
Ibandronic Acid (n=8)	60 (8)*	48 (6)	25.0 (4.0)	-2.7 (0.9)	-2.3 (0.9)	-2.4 (1.1)*
ZolindronicAcid I/V inj (n=17)	67 (8)	48 (5)	25.7 (4.3)	-2.8 (1.1)	-2.4 (1.1)	-2.8 (1.1)
Alendronate 10 mg daily(n=17)	67 (8)	48 (5)	25.3 (4.0)	-2.9 (1.1)	-2.4 (1.1)	-3.4 (1.1)
Alendronate 70 mg weekly (n=22)	66 (9)	48 (5)	25.7 (4.3)	-2.8 (1.0)	-2.4 (1.0)	-3.1 (1.0)
Risendronate (n=9)	67 (9)	48 (5)	25.5 (4.2)	-2.9 (1.0)	-2.4 (1.1)	-3.0 (0.9)
Total (n=101)	64 (9)	48 (5)	25.5 (4.2)	-2.6 (1.2)	-2.2 (1.1)	-2.7 (1.2)

\*p<0.05 between groups

**Table 3:** Treatment discontinuation

	CalciumvitamiD	HRT	Ibandronic Acid Monthly	Zolindronic Acid I/V inj/Yearly	Alendronate daily	Alendronate weekly	Risedronate daily	Total
Within6 months	14 (14.3)	56 (7.0)	71 (9.1)	236 (13.6)	16 (79.8)	131 (5.9)	110 (11.8)	1012 (10.3)
6–12 months	9 (5.4)	27 (3.4)	41 (5.3)	141 (8.2)	113 (6.6)	19 (0.9)	44 (4.7)	476 (4.8)
After12 months	3 (2.9)	100 (12.6)	15 (1.9)	122 (14.2)	76 (4.5)	4 (0.1)	23 (2.5)	389 (3.1)
Total	(22.7)	183 (23.0)	127 (16.3)	499 (28.7)	356 (20.9)	154 (6.9)	177 (19.0)	1877 (19.1)

aValues are the number of patients who discontinued the treatment; the corresponding percentage is given in parenthesis



**Figure 1:** Reasons for Discontinuation

**Table 4:** Compliance to

	Calciumvitamin D (%)	HRT (%)	Ibandronic Acid	Zolindronic Acid I/V inj	Alendronate daily (%)	Alendronate weekly (%)	Risedronate daily (%)	Total (%)
<30%	7.0	1.2	2.4	3.7	2.6	1.3	2.3	3.1
30–50%	14.0	1.4	4.7	8.7	6.8	1.6	5.0	6.4
50–80%	26.8	7.8	15.5	27.1	21.9	12.7	18.7	19.7

aValues are given as a percentage within each treatment

**Table 5:** Medical history and relative risk (RR) of discontinuation or low compliance (<50% drug taken). Multiple logistic regression analysis with data adjusted for treatment type

Variables	n (%)	RR for discontinuation (5–95% confidence interval)	RR for low compliance (5–95% confidence interval)
Early menopause	(21.9)	1.080 (96–1.23)	0.83* (0.73–0.95)
Family history for osteoporosis	(13.3)	0.950 (82–1.10)	0.75* (0.48–0.98)
Prevalent spine fracture	(17.3)	0.64* (0.43–0.82)	0.70* (0.61–0.80)
Bone measure not readily available	(20.6)	1.28* (1.05–1.59)	1.51* (1.22–1.85)
Osteoporosis (T-score <-2.5)	(43.7)	0.68* (0.56–0.82)	0.74* (0.62–0.88)
Corticosteroid therapy	(6.5)	0.69* (0.37–0.95)	0.82 (0.66–1.01)
Anti-inflammatory therapy	(14.3)	0.84* (0.65–0.99)	0.92 (0.80–1.06)
Benzodiazepin treatment	(6.5)	1.36* (1.23–1.45)	1.12 (0.92–1.36)
Gastro-protection therapy	(11.0)	1.24* (1.11–1.34)	1.17* (1.00–1.37)

## DISCUSSION

This is the largest survey to date that has been carried on treatment adherence to osteoporosis treatment. The mean discontinuation rate was 19%, the same proportion as that observed by Tosteson but over a mean period of follow up of only 7 months rather than the 14 months of our study.<sup>[8]</sup> The treatment persistence we observed may have been overestimated because the discontinuation rate is likely to be higher in the unknown number of patients who had a prescription 1 year prior to the beginning of our study but who did not return for follow-up. Both compliance and persistence were self-reported in the present study and not verified by objective tools. This may also be a source of overestimation of global adherence. In addition, our results are applicable only to patients in whom the osteoporosis treatment was prescribed on the basis of a densitometric evaluation. In a setting comparable to ours, 90.3% of the patients were still taking cyclical etidronate (Bisphosphonate) after 1 year, compared to 77.6% for once-daily doses of alendronate.<sup>[16]</sup> In studies carried out from data derived by health insurance or administrative

databases, adherence to treatment has been found to be considerably lower, ranging from 25 to 50%.<sup>[12,17,18,19,20]</sup> In general, treatment discontinuation rate varies considerably with type of treatment. In our series, the treatment adherence to HRT was at least twofold greater than that observed in other studies.<sup>[17,21,22]</sup> However, in these latter studies HRT was primarily prescribed to relieve the acute symptoms of menopause, even after screening patients for a recorded diagnosis for osteoporosis. This was not likely to be the case in our patients in whom the main motivation to treatment was the presence of osteoporosis.

The poorest performance was observed for intravenous Zolindronic acid, which in Bangladesh is registered but reimbursed lately for the treatment of osteoporosis, allegedly for lack of evidence of anti-fracture efficacy. This type of treatment is not extensively prescribed by GPs, perhaps for its high cost. However, this suggests a different approach between physicians and different specialties in how patients are educated and treated. The discontinuation rate for the other drugs was very similar, with the only remarkable



exception being ALN OW which showed a treatment persistence rate threefold higher than that of any other treatment. It has been shown that treatment adherence improves as the number of doses taken each day decreases,<sup>[23]</sup> and with weekly versus daily regimens.<sup>[20,24,25,26]</sup> Our results also provide further evidence that in comparison to daily dosing weekly dosing does improve persistence to treatment not only during controlled clinical trials but also in routine clinical practice. The most common reasons for treatment discontinuation were the appearance of side effects, which accounted for a quarter of all cases. This proportion is considerably lower than the 80% reported by Tosteson et al.<sup>[8]</sup> However, our questionnaire provided patients a broader range of possible causes than did that of Tosteson et al., including cost, inconvenient dosing, advice from other specialists, and these alternatives were frequently chosen by patients. One should recognize that the causes of inadequate treatment adherence may differ considerably depending on cultural and economic conditions. For example, lack of motivation may largely depend on the prestige of the prescriber or on the clinical relevance attributed to the disease under different cultural conditions. Thus, Zolindronic Acid, which was a little prescribed by only specialist not GPs, was discontinued first for lack of motivation and only thereafter for the inconveniences related to the intravenous administration. Cost may be a problem when the drug is not reimbursed early previous days. This was the case for ALN, RIS and Ibandronic acid when prescribed to patients without previous osteoporotic fractures or for not all treated patients. The main reason of

discontinuation of HRT was the fear of side effects, since the study was carried out at the time of the first media reports on the results of the Women's Health Initiative study.<sup>[27]</sup> Daily dosing with RIS and ALN, with their complex dosing instructions, were initially considered by several patients to be inconvenient and then often discontinued. This cause of discontinuation was, however, possibly also driven by the advertised availability of the weekly formulation of ALN. An important strength of our study is the possibility of identifying the risk factors for treatment discontinuation. Persistence to treatment was strongly related to factors that are likely to increase treatment motivation, such as: previous vertebral fractures, corticosteroid therapy, densito-metric evidence of osteoporosis, the ready availability of a bone measurement. The increased persistence to osteoporosis treatment observed in patients on chronic NSAID is possibly explained by the high prevalence of vertebral fracture among these patients ( $\chi^2 = 17.1$ ;  $p < 0.001$ ). The use of benzodiazepines and gastro-protective agents was a predictor of poor treatment persistence, possibly in relationship with the underlying co-morbidity. Somewhat surprisingly, age was not a predictive factor, even when analyzed individually in the logistic regression analysis. This may be explained by the balancing of decreasing general adherence with advancing age and the increased motivation to treatment for the severity of the disease. We also evaluated treatment compliance among patients who did not discontinue therapy. The compliance was rather poor for CaVitD supplements, with only one-half of the patients taking >80% of the prescribed doses, and, a sex expected, particularly high for HRT. Of

relevance is the significantly greater treatment compliance for ALN OW therapy versus all other bisphosphonates. This indicates that this treatment regimen is associated not only to increased persistence but also to greater compliance. Treatment compliance was poorer in patients suffering gastro-intestinal problems, but was enhanced by the ready availability of bone measurements with values within the range of osteoporosis. This is in agreement with previous reports that showed that those who understood their bone densitometry results were more likely to fill their prescriptions.<sup>[8,28,29]</sup> Even though the global adherence to treatment (i.e.: both persistence and compliance) was strongly related to the type of prescriber, this seems to have been driven mostly by the strong interaction between prescriber and nature of type of treatment, adherence remained significantly poorer for patients of GPs and Orthopaedic surgeons, primarily due to a lack of adequate

motivation. This is in agreement with a recent study showing that patients of GPs were more likely to discontinue their medications than the patients of internists.<sup>[29]</sup>

## CONCLUSIONS

In conclusion, the type of treatment given was the most important factor of both persistence and compliance to treatment in this large study of Bangladeshi osteoporotic women, with a clear preference for ALN OW. Treatment adherence was notably low for CaVitD, underlining the need to develop innovative methods of giving supplements, particularly vitamin D. The major causes for treatment termination were adverse effects and a lack of desire, with patients with severe and well-documented osteoporosis having the highest treatment adherence. The clinical implications of this form of treatment observance, as well as the financial consequences, require further investigation.

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