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ORIGINAL ARTICLE

Persistence and compliance to osteoporosis therapy in a fracture liaison service: a prospective cohort study

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Abstract

Summary Persistence and compliance to osteoporosis medications aiming to prevent fragility fractures are essential for fracture prevention, but are suboptimal in the population. A Fracture Liaison Service with a systematic follow-up led to ongoing therapy and optimal drug compliance for more than half of treated patients over 2 years.

Purpose Fracture Liaison Services (FLS) have the potential to improve persistence and compliance to osteoporosis therapy. We aimed to assess patterns of drug use in a high-level intervention FLS.

Methods Women and men (≥ 40 years) with a fragility fracture were recruited in a FLS, where osteoporosis therapy was prescribed if appropriate. Based on claims data, patients who filled their prescription in the 3-month period following baseline were selected. The 1- and 2-year persistence rates were measured using survival analysis. In non-persistent subjects, 1-year treatment re-initiation was measured. The 1- and 2-year compliance levels were measured, using the proportion of days covered (PDC ≥ 80% = compliant). Regression analyses were performed to identify predictors of non-persistence/compliance.

Results Out of 332 subjects with complete drug insurance coverage, 297 (89.5%) were prescribed osteoporosis therapy by the FLS, and 275 (92.6%) were dispensed. Two hundred sixty participants (86.9% female; mean age 65.6 years) were selected for having filled a prescription inside 3 months after baseline. The 1- and 2-year persistence rates were 66.4% and 55.6%, respectively. Treatment re-initiation was observed in 56% of non-persistent patients. PDC was ≥ 80% in 64.2% for 1 year and 62.5% for 2 years. Older and younger age, smoking, higher spine bone mineral density, lower major FRAX risk, and missing follow-up visits were predictors of non-persistence and/or non-compliance.

Conclusions After 2 years in a high-level intervention FLS, more than half the treated participants were persistent and compliant to treatment. Comparative effectiveness studies must be undertaken to determine whether this intervention is an improvement over usual care.

Keywords Persistence · Compliance · Fragility fracture · Osteoporosis · Fracture liaison service

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Introduction

Osteoporosis is a chronic, silent disease causing a progressive loss of bone mass, due to aging, menopause, and other factors, whose only manifestation are fractures [1]. Several treatments inhibit bone turnover or promote bone formation to help prevent fragility fractures. These agents are prescribed orally, as first-line treatment, and often percutaneously, as second-line treatment. They can decrease the risk of vertebral, hip, and non-vertebral fractures by 30 to 70% [2, 3]. There is a high prevalence of osteoporosis-related fractures, and 20 to 30% of patients will be properly investigated, assessed, and receive treatment recommendations [4–6]. Regardless, several real-world studies report that even when fragility fracture patients successfully begin osteoporosis treatment, persistence and compliance remain suboptimal. Indeed, 50% discontinue therapy 12 months after initiation and compliance is poor [7–9]. This represents a real public health issue since the correlation between optimal compliance to preventive agents and the reduction of fracture risk has been clearly established [10–13].

Fracture liaison services (FLS) and other secondary fracture prevention (SFP) programs have proven successful at identifying, investigating, and recommending treatment for such cases [14–16]. These programs vary greatly when it comes to the type of intervention, management, and length of follow-up, but represent a potential pathway for improved drug use over time. There is limited evidence that such secondary fracture prevention interventions are effective at increasing persistence and compliance rates in fracture patients based on real-time drug dispensation data [14, 17–20]. The present study aimed to report on osteoporosis medication initiation, persistence, and compliance in participants of a type A FLS [21] with a systematic longitudinal follow-up (2 years).

Materials and methods

Study population

The present study is based on the Lucky Bone™ Program prospective cohort study—a multidisciplinary follow-up of 532 women and men 40 years or older having sustained a fragility fracture, recruited in two outpatient orthopedic clinics between 2010 and 2013. The program was designed according to Osteoporosis Canada guidelines [22] for the management of osteoporosis and fragility fractures, and modeled as an outpatient-based FLS. Patients were identified, investigated, initiated on preventive therapy, and integrated to a longitudinal and systematic follow-up, with visits at 3, 6, 12, 18, and 24 months. Detailed design, methodology, and intervention details of the Lucky Bone™ Program were published previously [23].

The study was approved by the CIUSSS Nord-de-l'Île de Montréal ethics research committee and by the Commission d'Accès à l'Information du Québec. Enrolled patients provided signed informed consent.

Clinical and administrative data sources

The present study was conducted using clinical and administrative data. Clinical data included age, gender, height, weight, body mass index (BMI), incident fracture site measured at baseline through medical records, patient-reported prior history of fractures, medication history as reported by patients or from medical files, prescribed medications for osteoporosis at baseline by the FLS, patient-reported lifestyle habits (alcohol use, smoking status, physical activity), assessment of the 10-year major and hip fracture risk with the FRAX® tool [24], and bone mineral density (BMD) test results. Incident fracture sites were categorized as major or other. Those of the hip, the spine, the wrist, and the proximal humerus were considered as major fractures, and the remaining sites were considered as other fractures [25]. BMD was measured at the lumbar spine and the femoral neck using dual-energy X-ray absorptiometry (DXA) and the World Health Organization's definition of osteoporosis was used [26, 27]. Participants went to the radiology clinic of their choice, as no DXA machine was available on site. For each patient, the result of the DXA (T-score at spine and femoral neck) was obtained from the radiologist report.

Administrative data was retrieved from the Régie de l'Assurance Maladie du Québec (RAMQ), Med-Echo and ReMed databases. The RAMQ provides data for medical services (all residents) and community pharmacies managed by public health services (residents aged $\geq$ 65 years, social assistance beneficiaries, and workers without a private drug insurance program) in the province of Québec, Canada. Med-Echo compiles hospitalization and ambulatory claims data. ReMed is a centralized information system on Québec community pharmacy data for privately covered residents [28]. ReMed pharmaceutical services data was retrieved for the 340 participants (63.9%) who gave consent. These databases provided data on diagnosis, medical procedures, prescription claims (date of purchase, drug name, dosage, form, quantity, and duration), hospitalization (site, start/discharge dates, duration, and diagnosis), and date of death. Medical services diagnoses claims are coded according to the International Classification of Disease (ICD), ninth revision, while hospitalizations diagnosis claims are coded according to ICD-9 up to March 31, 2006, and ICD-10 upon April 1, 2006. We retrieved administrative data for medical services and hospitalizations up to 5 years before the recruitment date, up to 1 year before for data from pharmacies, and for the duration of the study. For patients that withdrew from the study, administrative data was censored on the last visit date before withdrawal. Quebec

prescription claims databases were found to be accurate by previous pharmacoepidemiological studies [29].

Patient selection

The initiation of osteoporosis medications and calcium/vitamin D supplementation was reviewed for all patients with drug insurance data. Women and men with at least one prescription for a selected agent dispensed by a community pharmacy, according to pharmaceutical claims data over the 3-month period following cohort entry (baseline), were selected for analyses. This selection strategy was chosen to assess the impact of FLS follow-up on treatment use. Therefore, patients who filled their prescription > 3 months after baseline were excluded. Prescription dispensation was identified using drug identification numbers (DIN). Selected oral therapies were risedronate, alendronate, etidronate, raloxifene, or calcitonin. Injectable therapies were zoledronic acid, denosumab, and teriparatide. The date of the first dispensation was set as the index date and was defined as treatment initiation in the FLS.

Assessment of osteoporosis drug usage in the FLS

Outcomes included (1) treatment initiation, (2) persistence rate to treatment over 1 and 2 years after initiation, (3) treatment re-initiation within 1 year after discontinuation, and (4) compliance level over 1 and 2 years after treatment initiation. Calcium and vitamin D supplementation was a secondary outcome. The authors defined and interpreted persistence and compliance according to Cramer et al.'s definition [30].

Persistence was defined as a continuous prescription refill over time, with a permissible gap between refills of 60 days, giving a cumulative persistence rate over 1 and 2 years after treatment initiation. Switching therapies was allowed. Censoring was set on death dates, first date of hospital stays of 15 days or more, the end of drug insurance coverage, and end of follow-up. Sensitivity analyses were performed (1) using 45 and 90 days as different permissible gaps and (2) by restricting the computation to oral therapies. The latter was done by censoring the use or the switch to injectable therapies and using a permissible gap between refills of 30 days. Patients categorized as non-persistent were included in a sub-analysis, where treatment re-initiation was measured as the dispensing of one of the selected agents within a year following discontinuation [31]. Non-persistent patients without complete 1-year drug insurance coverage after discontinuation were not included in this sub-analysis.

Compliance levels at 1 and 2 years were measured as a proportion of days covered (PDC). The PDC is defined as the number of days with medication over a pre-defined period of time to a maximum of 100% [31]. The PDC was measured considering that there could be periods of prescription overlap and assuming 100% compliance during hospital stays. Selected patients had to have complete drug coverage over 1 or 2 years after the index date. The compliance level was determined by dichotomizing the PDC with an 80% threshold, where patients with PDC $\geq$ 80% were deemed compliant [32]. Sensitivity analyses were conducted (1) with a 90% PDC threshold, (2) in oral therapies by subtracting the time imputable to the duration of injectable therapy prescriptions from the PDC calculation, and (3) in all patients that initiated treatment according to their specific follow-up time, instead of a steady 2-year period. For the last sensitivity analysis, the follow-up time was censored at the date of the end of drug insurance coverage, date of death, or end of follow-up. This final analysis made it possible to determine whether selecting patients with a complete 2-year drug coverage affected the PDC.

Identification of predictors of non-persistence and non-compliance

Potential predictors were selected based on the clinical possibility of influencing persistence and compliance in the FLS setting. They included age, gender, BMI, BMD T-scores, FRAX scores, physical activity status (considered active with at least 30 min of physical activity, from walking to intense-level sports, per week), smoking status (current smoker vs non-smoker), treatment-experienced (reported being under osteoporosis medication before the incident fracture event, yes/no), patient-reported prior fracture history (yes/no), the number of co-medications (categorized as 0–5 or > 5), alcohol consumption according to patients (yes/no), and index fracture site (major or other). The presence of specific comorbidities was ascertained using diagnostic codes (ICD) from medical services and hospitalization claims, in order to measure the Charlson Comorbidity Index (CCI) [33–35]. Finally, FLS visit attendance was also deemed of interest and defined as a dichotomous variable; all visits attended (27.7%) vs $\geq$ 1 visit missed (72.3%).

Statistical analysis

Baseline characteristics were presented as means with standard deviations for normal distributions, or medians with interquartile ranges for non-normal distributions. Subjects selected because of prescription dispensation inside the 3-month period after baseline were compared to participants whose first prescription dispensation was after this time window. Groups were compared using Chi-square tests for categorical variables and Student's *t* tests or Wilcoxon-Mann-Whitney tests for continuous variables. Osteoporosis medication and calcium/vitamin D supplementation initiation was measured using the proportion of subjects that filled their prescription among those that were handed a prescription in the FLS, with drug insurance coverage over different time-periods (3, 6, 12, and 24 months). The 1- and 2-year

cumulative persistence rates were measured using Kaplan-Meier analyses. A stratified analysis was undertaken to compare the 2-year cumulative persistence rate according to the FLS participation status, using a Log-rank test. We estimated hazard ratios (HR) and their 95% confidence intervals with Cox regression models to identify predictors of non-persistence, after verifying that the proportional hazard assumption was true. Predictors of non-compliance were estimated by measuring odds ratios (ORs) and their 95% confidence intervals with logistic regression models. For both regression methods, univariate models were used for each potential predictor, which were then selected to perform adjusted analyses when $p \leq 0.1$. Variables that the investigators considered clinically relevant could be forced into the adjusted models. Because of missing data for a few covariates (8.7–12.7%), multiple imputation with arbitrary logistic, discriminant, and predictive mean matching methods (FCS) were used (PROC MI and PROC MIANALYZE) by adding baseline complete covariates to imputation models, assuming data missing at random [36]. Statistical analysis system (SAS) software 9.4 (SAS Institute, Cary, NC) was used to perform analyses in an intention-to-treat fashion, and a p value ≤ 0.05 was deemed statistically significant (Bonferroni correction applied for multiple comparisons).

Results

Out of 373 participants with a prescription for osteoporosis medication dispensed during the 2-year follow-up period, 260 (69.7%) filled it in the first 3 months following baseline and were selected for subsequent analyses (Fig. 1). Mean age was 65.6 (± 11.0) years with a majority of female. Most subjects were osteopenic on BMD. A third of the cohort consumed alcohol, more than 70% were active, and almost 20% were current smokers. Thirty-five percent of subjects reported a history of prior fracture and nearly 23% indicated they had used osteoporosis medications before the incident fracture. A little over half the subjects had a CCI of one or more, and almost 47% used five medications or more. Close to 63% of participants had an incident fracture at a major site. These results are presented in Table 1. They also show that selected subjects consumed less alcohol and were less active than subjects with a prescription dispensed later in the follow-up. As expected, patients with a prescription dispensed later in the follow-up were less handed a prescription from FLS personnel at baseline and were prescribed injectable therapies more often ($p < 0.01$).

Initiation of osteoporosis medication and supplementation

Over the 2-year follow-up in the FLS, 332 subjects had complete drug insurance coverage, of which 286 (86.1%) filled

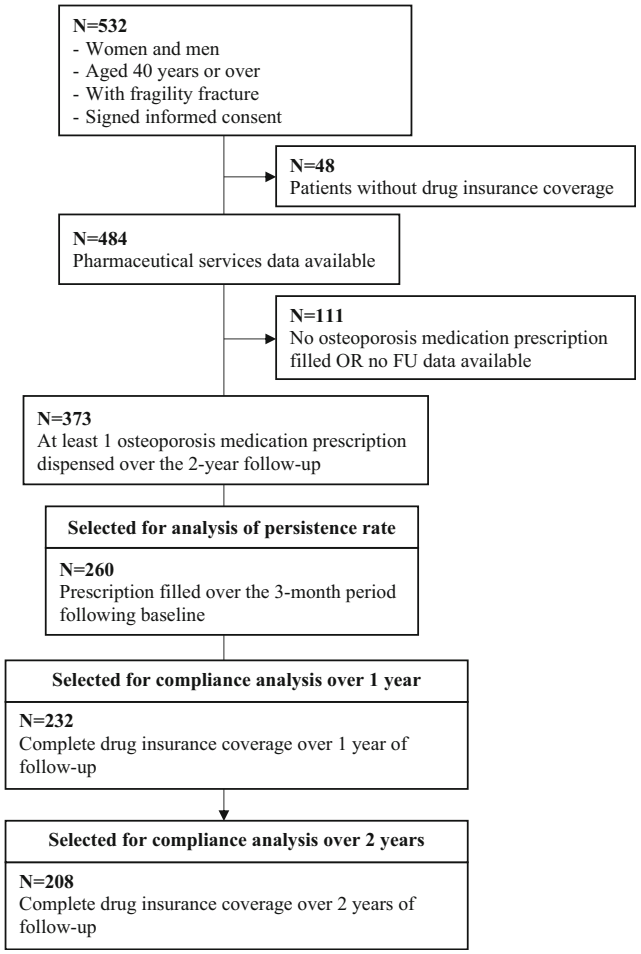

Fig. 1 Flow chart of patient selection. FU follow-up

their prescription at a community pharmacy at one time or another. Figure 2 shows that among the subjects with coverage, almost 90% were given a prescription for osteoporosis therapy by FLS personnel and, of these, close to 93% had it dispensed. Risedronate was the most frequently prescribed and dispensed agent at the initiation of treatment (> 70%), and 67 patients switched from oral to injectable therapy over 2 years (23.4%). In patients with complete drug coverage, 305 (89.4%) received calcium/vitamin D supplementation from a community pharmacy over the 1-year follow-up period (n = 341), and 93.7% (311/332) over the 2-year follow-up period.

Persistence, re-initiation, and compliance

The 1- and 2-year persistence rates were 66.4% (95% CI [60.0–72.0]) and 55.6% (95% CI [49.0–61.7]), respectively (Fig. 3). When the persistence rate was measured for the group of subjects that was handed a prescription in the FLS (n = 226 (86.9%)), the results increased marginally [1 year 68.2%, 95% CI (61.5–74.0); 2 years 57.1%, 95% CI (50.1–63.6)]. There was a statistically significant difference in persistence rates between patients that attended all visits compared to those

Table 1 Comparison of baseline characteristics between FLS participants with osteoporosis therapy dispensed before and after 3 months following baseline assessment

Variables	Number of patients (%)		*p* value
	Prescription dispensed 3 months	Prescription dispensed > 3–24 months	
Total patients	260 (69.7)	113 (30.3)	
Number female	226 (86.9)	95 (84.1)	0.465
Age, mean (±SD)	65.6 (11.0)	64.4 (10.3)	0.317
40–59	83 (31.9)	40 (35.4)	0.636
60–69	91 (35.0)	40 (35.4)	
70–79	51 (19.6)	23 (20.3)	
80+	35 (13.5)	10 (8.9)	
Body mass index†	260 (100.0)	112 (99.1)	
Mean (±SD)	25.9 (5.4)	26.5 (5.7)	0.386
Referral to a specialist	66 (25.4)	29 (25.7)	0.955
Femoral BMD†	229 (88.1)	109 (96.5)	
Mean (±SD)	− 1.66 (0.93)	− 1.77 (0.81)	0.291
> − 1.0	48 (20.9)	14 (12.8)	0.173
<− 1.0 to > − 2.5	144 (62.9)	78 (71.6)	
<− 2.5	37 (16.2)	17 (15.6)	
Spine BMD†	229 (88.1)	108 (95.6)	
Mean (±SD)	− 1.76 (1.32)	− 1.78 (1.33)	0.859
> − 1.0	63 (27.5)	25 (23.2)	0.685
<− 1.0 to > − 2.5	96 (41.9)	47 (43.5)	
<− 2.5	70 (30.6)	36 (33.3)	
Major FRAX†	258 (99.2)	113 (100.0)	
Median (IQR)	12.0 (8.0–17.0)	12.0 (7.5–18.0)	0.979
< 10%	112 (43.4)	46 (40.7)	0.880
10–19%	93 (36.1)	42 (37.2)	
> 20%	53 (20.5)	25 (22.1)	
Hip FRAX†	258 (99.2)	113 (100.0)	
Median (IQR)	1.9 (0.7–4.5)	2.2 (0.7–5.0)	0.813
< 3%	161 (62.4)	69 (61.1)	0.806
> 3%	97 (37.6)	44 (38.9)	
Alcohol consumption†	259 (99.6)	112 (99.1)	
Yes	87 (33.6)	54 (48.2)	0.008
Physical activity†	226 (86.9)	106 (93.8)	
Active[a]	162 (71.7)	87 (82.1)	0.041
Physical activity level			
Little	25 (15.4)	13 (14.9)	0.987
Low	65 (40.1)	35 (40.2)	
Moderate	59 (36.4)	33 (37.9)	
Intense	13 (8.0)	6 (6.9)	
Current smoking†	257 (98.8)	112 (99.1)	
Yes	50 (19.5)	19 (17.0)	0.573
Past smoking†	195 (75.0)	88 (77.9)	
Yes	86 (44.1)	42 (47.7)	0.571
Prior fracture history	91 (35.0)	33 (29.2)	0.275
Treatment-experienced‡	59 (22.7)	21 (18.6)	0.374
CCI category§			
0	113 (43.5)	54 (47.8)	0.440
> 0	147 (56.5)	59 (52.2)	
Number of medications			
0–5	138 (53.1)	70 (61.9)	0.113
> 5	122 (46.9)	43 (38.1)	
Incident fracture site¶			
Major	164 (63.1)	72 (63.7)	0.906
Other	96 (36.9)	41 (36.3)	
Baseline prescription from FLS¥			
No	34 (13.1)	50 (44.2)	< 0.001
Yes	226 (86.9)	63 (55.8)	
Agent dispensed£			
Risedronate	206 (79.2)	63 (55.8)	< 0.001
Other oral therapies	45 (17.3)	13 (11.5)	
Injectable therapies	9 (3.5)	37 (32.7)	

BMD bone mineral density, *CCI* Charlson comorbidity index, *IQR* interquartile range, *SD* standard deviation

† Number of subjects with data available

[a] At least 30 min of physical activity (from walking to intense-level sports) per week

‡ Exposed to osteoporosis medication before the initial incident fracture (patient-reported)

§ Measured using claims data from provincial databases, up to 5 years before baseline

¶ Major fracture sites include the hip, spine, wrist, and humerus

¥ Osteoporosis treatment prescribed and handed by FLS personnel at baseline

£ First prescription after FLS baseline. Dispensed in community pharmacies, identified through pharmaceutical claims database

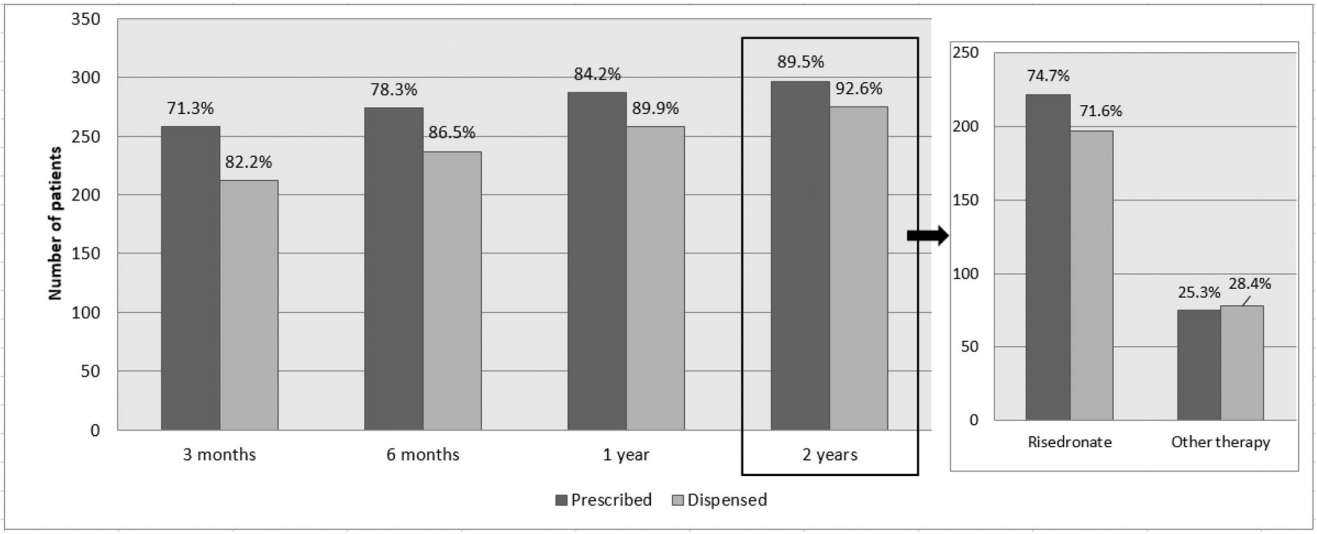

Fig. 2 Cumulative distribution of prescriptions for osteoporosis drugs and type of therapy handed in the FLS (prescribed) and filled in community pharmacies (dispensed) over the 2-year follow-up in a fracture liaison service. Data to identify "prescribed" prescriptions were obtained from the clinic's FLS database. Data to identify "dispensed" prescriptions were obtained from the pharmaceutical claims administrative RAMQ database

who missed at least one (Fig. S1, Online resource 1), with a lower persistence rate for the latter ($p = 0.01$). Sensitivity analyses showed a small variation in persistence rates when the grace period was set at 45 days [1 year 64.1%, 95% CI (57.7–69.7); 2 years 53.7%, 95% CI (47.1–59.8)] and 90 days [1 year 69.8%, 95% CI (63.6–75.1); 2 years 59.4%, 95% CI (52.9–65.4)], and when the analysis was restricted to oral agents exclusively [1 year 60.7%, 95% CI (53.8–66.8); 2 years 50.4%, 95% CI (43.2–57.2)]. From a hundred discontinuing patients (non-persistent) with complete drug coverage, 56 re-initiated treatment within 1 year after discontinuation.

Compliance levels (PDC $\geq$ 80%) at 1 and 2 years after initiation were 64.2% and 62.5%, respectively (Table 2). Median PDCs were > 90. Sensitivity analyses showed that when using a PDC level of 90%, 1- and 2-year compliance levels dropped to 56.5% and 51.0%, respectively. Compliance levels were similar for exclusive oral therapy use (1 year 62.8%; 2 years 59.0%). When using patient-specific follow-up time, the compliance level did not vary greatly (61.7% after a mean follow-up time of 671.9 (± 163.5) days). Persistence rate and compliance levels correlated significantly ($r = 0.851$, p value < 0.001).

Predictors of persistence rate and compliance level

Predictors of non-persistence and non-compliance are presented in Table 3. Adjusted regressions showed that being aged between 40 and 59 years (aHR = 2.03, 95% CI [1.19–3.48]) or 80+ years (aHR = 2.55, 95% CI [1.15–5.66]) compared to 60–69 years, being a current smoker (aHR = 2.59, 95% CI [1.66–4.06]), and missing a FLS visit (aHR = 1.93, 95% CI [1.20–3.11]), were significant predictors of non-persistence. Analyses also revealed that higher major fracture risk according to FRAX (11–19% vs $\leq$ 10%) was predictive of better

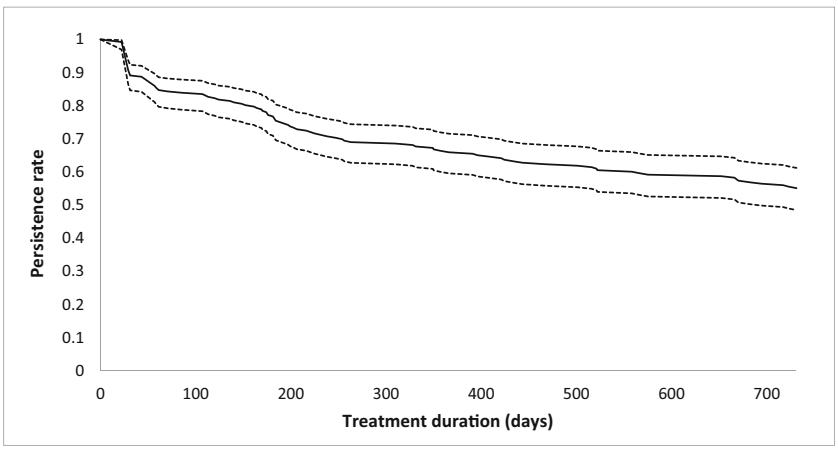

Fig. 3 Survival curve (dark line) and 95% confidence interval (dashed lines) of persistence rate to osteoporosis treatment over a 2-year follow-up in a fracture liaison service

Table 2 Proportion of days covered to measure compliance levels over a 2-year follow-up period after treatment initiation in a fracture liaison service

	1 year	2 years	Variable duration[†]
Number covered[‡]	232	208	253
Mean PDC (±SD)	77.6 (28.3)	75.5 (30.0)	74.9 (30.7)
Median PDC (IQR)	92.3 (59.1–99.4)	91.3 (57.8–98.4)	92.0 (57.8–98.8)
PDC ≥ 80%, *n* (%)	149 (64.2)	130 (62.5)	156 (61.7)
PDC ≥ 90%, *n* (%)	131 (56.5)	106 (51.0)	129 (51.0)
Oral drugs only (PDC ≥ 80%), *n* (%)[§]	140 (62.8)	118 (59.0)	–

IQR interquartile range, *PDC* proportion of days covered, *SD* standard deviation

[†] Mean follow-up time of 671.9 (± 163.5) days

[‡] With drug insurance coverage over specific time periods

[§] Because of the exclusion of patients taking exclusively injectable drugs, denominators were $n = 223$ for 1 year and $n = 200$ for 2 years

persistence (aHR = 0.54, 95% CI [0.32–0.90]), and there was a tendency toward a higher spine BMD associated with non-persistence (aHR = 1.15, 95% CI [0.99–1.34]). This association was statistically significant to predict compliance with an osteoporotic spine BMD [*T* score ≤ − 2.5, aOR = 0.39, 95% CI (0.15–0.98)]. Smoking [aOR = 4.89, 95% CI (2.09–11.42)] and missing a FLS visit [aOR = 2.89, 95% CI (1.41–5.91)] were also significant predictors of non-compliance.

Discussion

Persistence and compliance to osteoporosis therapy are essential to achieve optimal use and risk reduction of osteoporosis-related fractures. Hence, it is important that secondary fracture prevention programs focus on improving these parameters in patients.

The FLS described here, with a high intensity intervention program based on detection, investigation, treatment, and longitudinal monitoring, aimed, among multiple objectives, to improve all aspects of treatment, including initiation, persistence rate, and compliance level. After 2 years of follow-up, almost 90% of FLS patients received a prescription for a preventive therapy, and nearly 93% had it dispensed in a community pharmacy. There are numerous publications on osteoporosis treatment initiation and most show improved results with SFP programs over usual care. However, prescription, dispensation, and patient-reported intake are not clearly dissociated in most studies [17, 21, 37]. Naranjo et al. found results similar to those of the present study for prescription delivery (71.5%) and initiation (82%) after 3 months in a type A FLS with systematic telephone follow-up, although there was a reduction in treatment initiation after 12 months (72%) [38]. Regarding calcium and vitamin D supplementation, results clearly show the FLS's impact; in Quebec (Canada); it is possible to buy such supplements over-the-counter without a prescription. However, calcium carbonate and vitamin D3 were automatically prescribed to FLS participants, and almost 94% of patients had this prescription dispensed over the 2-year follow-up.

Population-based studies in Canada and the USA show that 2-year persistence rates vary between 26 and 35% and compliance levels (MPR ≥ 80%) between 26 and 52% [7, 39]. The results of this study show that slightly more than half of patients were still on therapy after 2 years, and approximately 60% of patients filled at least 80% of their medication over this time period. Interestingly, more than half of non-persistent patients re-initiated treatment in the year following discontinuation. To the best of our knowledge, only Ganda et al. have studied both persistence and compliance in a type A FLS using administrative data. They reported 1- and 2-year persistence rates of 82% and 64%, respectively, using a 90-day permissible gap between refills, during the systematic follow-up of a cohort of fractured women and men (45 years or older), part of a SFP group. Patients with a MPR ≥ 80% after 2 years reached 49% in the intervention group, and their 2-year results were similar to those reported here, when using the same permissible gap for persistence. However, the present study found a higher compliance level, which could be explained by discrepancies in the measurement methods [19]. A controlled trial, very recently conducted in Canada on fractured (upper extremities) women and men aged > 50 years, reported results on osteoporosis medication compliance after 2 years of follow-up similar to the present study. Participants were randomized in two interventional groups with systematic follow-up (physician education vs nurse-led). The primary outcome was 1- (~ 79%) and 2-year (53–67%) compliance levels (> 80% pills consumed), which used patient-reported and pharmacy dispensing records for confirmation [40]. Another recent systematic review and meta-analysis reported a 57% unweighted average compliance level with a 0.22 (0.13–0.35) absolute risk difference in favor of intervention groups, compared to controls (follow-up time between 3 and 48 months). It should be noted that there was

Table 3 Predictors of non-persistence and non-compliance to osteoporosis therapy during 2 years in a fracture liaison service

Predictors	Non-persistence				Non-compliance			
	Crude		Adjusted		Crude		Adjusted	
	HR	95%CI	HR	95%CI	OR	95%CI	OR	95%CI
Gender								
Female	Reference		Reference[†]		Reference		Reference[†]	
Male	0.90	(0.51–1.61)	0.82	(0.44–1.53)	1.09	(0.48–2.47)	0.93	(0.36–2.45)
Age groups (years)								
60–69	Reference		Reference		Reference		Reference	
40–59	2.47	(1.53–3.98)	2.03	(1.19–3.48)	2.32	(1.18–4.54)	2.19	(0.93–5.13)
70–79	1.26	(0.69–2.29)	1.31	(0.68–2.50)	0.85	(0.37–1.99)	0.96	(0.37–2.52)
80+	1.84	(0.98–3.48)	2.55	(1.15–5.66)	1.38	(0.51–3.78)	2.17	(0.61–7.70)
Spine BMD	1.12	(0.96–1.30)	1.15	(0.99–1.34)[†*]	–	–	–	–
> − 1.0	–	–	–	–	Reference		Reference	
≤ − 1.0 to > − 2.5	–	–	–	–	0.59	(0.29–1.19)	0.63	(0.29–1.38)
≤ − 2.5	–	–	–	–	0.46	(0.21–0.99)	0.39	(0.15–0.98)
Major FRAX								
≤ 10%	Reference		Reference		Reference		Reference	
11–19%	0.48	(0.30–0.76)	0.54	(0.32–0.90)	0.53	(0.28–0.99)	0.80	(0.36–1.77)
≥ 20%	0.76	(0.46–1.24)	0.81	(0.39–1.70)	0.60	(0.27–1.34)	0.95	(0.29–3.13)
Incident fracture site[a]								
Other	Reference		Reference[†]		Reference		Reference[†]	
Major	0.97	(0.65–1.44)	0.96	(0.63–1.46)	0.78	(0.43–1.39)	0.67	(0.34–1.32)
Smoking status[‡]								
Non-smoker	Reference		Reference		Reference		Reference	
Smoker	2.24	(1.47–3.40)	2.59	(1.66–4.06)	3.37	(1.64–6.94)	4.89	(2.09–11.42)
Number of medications[‡]	–	–	–	–	0.94	(0.88–0.99)	0.94	(0.88–1.01)*
0–5	Reference		Reference		–	–	–	–
> 5	0.62	(0.42–0.91)	0.71	(0.46–1.09)	–	–	–	–
Initial prescription delivered in the FLS[¶]								
No	Reference		Reference		–	–	–	–
Yes	0.61	(0.36–1.04)	0.65	(0.37–1.13)	–	–	–	–
Treatment-experienced[‡§]								
New user	–	–	–	–	Reference		Reference	
Treatment-experienced	–	–	–	–	0.52	(0.25–1.11)	0.74	(0.30–1.83)
Follow-up attendance[¥]								
All visits	Reference		Reference		Reference		Reference	
≥ 1 missed visit	1.81	(1.14–2.88)	1.93	(1.20–3.11)	2.29	(1.22–4.32)	2.89	(1.41–5.91)

BMD bone mineral density, *CI* confidence interval, *FLS* fracture liaison service, *HR* hazard-ratio, *OR* odds ratio

Multiple imputation method ($n = 50$) performed on spine BMD, major FRAX, and smoking status to obtain estimates free of missing data

[*] Continuous outcomes

[†] Forced into the adjusted models

[a] Major fracture sites include the hip, spine, wrist, and humerus

[‡] Patient-reported

[¶] Osteoporosis therapy prescribed and handed by FLS personnel

[§] Exposed to osteoporosis medication before the initial incident fracture

[¥] "All visits" refers to patients that attended all follow-up visits, "missed visits" refers to patients that missed at least one follow-up visit over 2 years (3, 6, 12, 18, and 24 months)

a high level of heterogeneity between studies ($I^2 = 75.8$), with observational studies as well as randomized controlled trials included in the meta-analysis [17].

Being younger than 60 years or older than 80 years, smoking and increased spine BMD were found to predict non-persistence and/or non-compliance. Smoking has often been associated to an increased risk for low osteoporosis medication compliance [41]. Because of the time and costs associated with a preventive pharmacological treatment, a higher BMD result could explain a poorer persistence and compliance. Indeed, although fragility fractures are a criterion to initiate preventive pharmacological treatment, patients knowing that they do not suffer any bone fragility according to DXA test results, might not be as motivated to pursue treatment. Bessette et al. also report a similar interrelation, where a lower BMD increased the likelihood of treatment for osteoporosis [42]. Abovementioned predictors are probably not only a consequence of the FLS, but the predictor attributable to the FLS was high participation levels to follow-up visits, where risks of non-persistence and non-compliance were decreased. However, this could also be the result of a healthy-user bias. To verify this hypothesis, we compared baseline characteristics between patients with perfect visit compliance vs those with at least one missed visit (Table S1, Online resource 1). Patients in the "missed visits" group were older, had a higher FRAX 10-year estimation of fracture risk, and a higher proportion of patients with a CCI score $\geq$ 1, indicating more important comorbidities than patients with a perfect attendance record. However, when losses to follow-up were excluded, the CCI was similar between groups and a significant risk of non-persistence [aHR = 1.83, 95% CI (1.11–3.02)] and non-compliance [aOR = 2.93, 95% CI (1.38–6.21)] in the "missed visits" group remained. Moreover, multivariate regression models were adjusted for age and major FRAX. Consequently, despite the remaining risk for bias, results suggest that the intervention can be more successful, in terms of drug use, if its stakeholders are able to retain participants and see them systematically over time. The challenge now will be to verify whether such management is possible in a real-world setting, especially considering the high number of visits per year required.

There are some limitations to this study. Because osteoporosis-related fractures increase the risk of morbidity and mortality, the investigators decided to provide FLS access to all eligible patients. Consequently, there was no control group for comparison and adequate evaluation of the impact of the FLS on osteoporosis medication use over 2 years. Moreover, follow-up time varied between participants because of loss to follow-up. The use of administrative data from pharmacy services made it possible to measure prescription dispensation in real time and provided a good indication of drug use. Although it is impossible to know whether an individual actually took the dispensed medication, ongoing prescription renewal can be a good indicator of treatment persistence [19]. Another advantage of using pharmaceutical claims data to measure drug use is that it is less prone to information bias, compared to patient-reported data [43, 44]. The follow-up period was limited to 2 years for this study, which might not be sufficient to assess the FLSs' impact on the chronicity of osteoporosis. Finally, to exclude the possibility of behavior changes imputable to the visits and their impact on persistence and compliance, only patients who initiated treatment during the 3-month period after baseline were included in the analysis.

Conclusion

The implementation of a high intensity FLS with a systematic follow-up in an outpatient setting, resulted in a high percentage of osteoporosis medication initiation over time, and more than half of the subjects being persistent and compliant to therapy 2 years after initiation. Furthermore, the percentage of treatment re-initiation after discontinuation was over 50%. Results also highlight the importance of a closely monitored follow-up, with facilitated access to care, making it easy for patients to attend visits and improve FLS performance in terms of drug use over time. Large comparative effectiveness studies with real-time drug dispensation data are now needed to determine if such type A FLSs with a longitudinal follow-up represent a true improvement over usual care, regarding persistence and compliance.

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Compliance with ethical standards

Conflict of interest Senay and Perreault declare that they have no conflict of interest. Delisle reports support for personal fees from Amgen Canada and Eli Lilly outside of the conducted work. Morin reports research grants from Amgen Canada and Merck outside of the conducted work. Fernandes reports grants from Eli Lilly during the conduct of this study, and grants from Baxter outside of the conducted work.

All procedures performed in this study involving human participants were in accordance with the ethical standards of the CIUSSS Nord de l'Ile de Montréal ethic research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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